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<b>(21) International Application Number:</b> PCT/US00/06902 <b>(22) International Filing Date:</b> 16 March 2000 (16.03.00) <b>(30) Priority Data:</b> 60/125,177 19 March 1999 (19.03.99) US 60/125,145 19 March 1999 (19.03.99) US 60/125,338 19 March 1999 (19.03.99) US 09/357,404 20 July 1999 (20.07.99) US <b>(71) Applicant:</b> PARKER HUGHES INSTITUTE [US/US]; 2665 Long Lake Road, St. Paul, MN 55113 (US). <b>(72) Inventors:</b> UCKUN, Fatih, M.; 12590 Ethan Avenue North, White Bear Lake, MN 55110 (US). LIU, Xing-Ping; 1010 6th Street S.E., Minneapolis, MN 55414 (US). NARLA, Rama, K.; 1270 Larpenner Avenue, St. Paul, MN 55113 (US). <b>(74) Agent:</b> DAIGNAULT, Ronald, A.; Merchant & Gould P.C. P.O. Box 2903, Minneapolis, MN 55402-0903 (US).			<b>(81) Designated States:</b> AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), DM, DZ, EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (Utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> QUINAZOLINES AND THERAPEUTIC USE THEREOF			
<b>(57) Abstract</b>  Quinazoline compounds and methods for the treatment of cancer and for the treatment of allergic reactions.			

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## QUINAZOLINES AND THERAPEUTIC USE THEREOF

### Field of the Invention

This application relates to quinazoline compounds, compositions and  
5 therapeutic methods for the treatment of cancers and treatment of allergic disorders  
by administering quinazoline compounds.

### Background of the Invention

Quinazoline compounds have been suggested as useful compounds in the  
10 treatment of cell growth and differentiation characterized by activity of the human  
epidermal growth factor receptor type2 (HER2). See, for example, Myers et.al., U.S.  
Patent No. 5,721,237. Some quinazoline derivatives have been suggested as useful  
as anti-cancer agents for the treatment of specific receptor tyrosine kinase-  
expressing cancers, especially those expressing epithelial growth factor (EGF)  
15 receptor tyrosine kinase. See, for example, Barker et. al., U.S. Patent No. 5,457,105.

It is generally taught that quinazolines exert their anti-tumor effects via tyrosine  
kinase inhibition. However, while some quinazoline compounds inhibit the growth  
of brain tumor cells, others with equally potent tyrosine kinase inhibitory activity fail  
to do so (Naria et.al., 1998, *Clin. Cancer Res.* 4:1405-1414; Naria et.al., 1998,  
20 *Clin. Cancer Res.* 4:2463-2471).

Several tumors expressing EGF receptors are not killed by quinazoline  
compounds, whereas some tumors not expressing EGF receptors are. Thus, the  
cytotoxic activity of quinazoline compounds cannot be attributed to the compound's  
tyrosine kinase inhibitory activity, and particularly not to the compound's ability to  
25 inhibit EGF receptor tyrosine kinase. A chemical structure-activity relationship  
determining the anti-cancer activity of quinazoline derivatives has not been  
established.

Novel quinazoline compounds may provide potent new therapeutic  
molecules for the treatment of disorders such as cancers.. Methods of using both  
30 known and novel quinazoline compounds that employ an understanding of  
structure-function relationships are needed.

### Summary of the Invention

A series of quinazoline compounds were synthesized and analyzed  
35 for therapeutic activities, including anti-cancer activities, particularly against EGR

receptor-negative leukemias. Specific quinazoline compounds of the invention were found to possess potent and specific tyrosine kinase inhibitory activities affecting cell proliferation and survival. Quinazoline compounds of the invention are demonstrated as useful for the treatment of specific tumors, including breast  
5 tumors, brain tumors, and leukemias, particularly EGF receptor-negative leukemias, and to be particularly useful in the treatment of multi-drug resistant leukemias.

The invention provides novel quinazoline compounds of formula I, as disclosed below, as well as therapeutic methods utilizing these compounds.

10

### **Brief Description of the Drawings**

Figures 1A-1C are graphs showing cytotoxic activity of fluoro-substituted dimethoxy quinazoline compounds (F-dmQ) against leukemic NALM-6 cells.

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Figures 2A-2C are graphs showing cytotoxic activity of F-dmQ on breast cancer BT-20 cells.

Figures 3A-3F are photographs showing induction of apoptosis in cancer cells by F-dmQ.

Figure 4 is a bar graph showing adhesive properties of various cancer cells to extracellular matrix proteins.

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Figures 5A-5F are bar graphs showing the effect of F-dmQ on cancer cell-adhesion to extracellular matrix (ECM) proteins.

Figures 6A-6E are photographs showing the effects of HI-P353 and HI-P364 on glioblastoma cell migration from spheroids.

25

Figures 7A and 7B are bar graphs showing the anti-invasive activity of fluoro-substituted quinazoline compounds (F-dmQ) against glioblastoma U373 and breast cancer MDA-MB-231 cells.

Figures 8A-8D are photographs showing depolymerization of actin stress fibers and microtubules by HI-P353.

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Figures 9A-9I are photographs showing inhibition of actin stress fiber formation in glioblastoma cells by HI-P154.

Figures 10A-10C are graphs showing the inhibition of cancer cell growth *in vivo* by the quinazolines of the invention.

**Detailed Description of the Invention****Definitions:**

The terms "quinazoline", "quinazoline compound", and "quinazoline derivative" are used interchangeably in this application to mean compounds of formula I.

All scientific and technical terms used in this application have meanings commonly used in the art unless otherwise specified. As used in this application, the following words or phrases have the meanings specified.

Halo is fluoro, chloro, bromo, or iodo. Alkyl, alkanoyl, etc., denote both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. (C<sub>1</sub>-C<sub>4</sub>)alkyl includes methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, and sec-butyl; (C<sub>1</sub>-C<sub>4</sub>)alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, and sec-butoxy; and (C<sub>1</sub>-C<sub>4</sub>)alkanoyl includes acetyl, propanoyl and butanoyl.

As used herein, "pharmaceutically acceptable carrier" means any material which, when combined with the compound of the invention, allows the compound to retain biological activity, such as the ability to potentiate antibacterial activity of mast cells and macrophages. Examples include, but are not limited to, any of the standard pharmaceutical carriers such as a phosphate buffered saline solution, water, emulsions such as oil/water emulsions, and various types of wetting agents. Compositions comprising such carriers are formulated by well known conventional methods (see, for example, Remington's Pharmaceutical Sciences, Chapter 43, 14th Ed., Mack Publishing Co., Easton, PA).

The term "conjugate" means a compound formed as a composite between two or more molecules. More specifically, in the present invention, the quinazoline derivative is bonded, for example, covalently bonded, to cell-specific targeting moieties forming a conjugate compound for efficient and specific delivery of the agent to a cell of interest.

The phrase "targeting moiety" means a molecule which serves to deliver the compound of the invention to a specific site for the desired activity. Targeting moieties include, for example, molecules that specifically bind molecules on a specific cell surface. Such targeting moieties useful in the invention include anti-cell surface antigen antibodies. Cytokines, including interleukins and factors such as

granulocyte/macrophage stimulating factor (GMCSF) are also specific targeting moieties, known to bind to specific cells expressing high levels of their receptors.

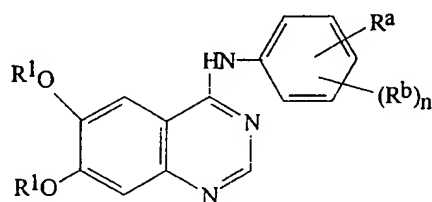
The term "prodrug moiety" is a substitution group which facilitates use of a compound of the invention, for example by facilitating entry of the drug into cells or administration of the compound. The prodrug moiety may be cleaved from the compound, for example by cleavage enzymes *in vivo*. Examples of prodrug moieties include phosphate groups, peptide linkers, and sugars, which moieties can be hydrolyzed *in vivo*.

"inhibit" means to reduce by a measurable amount, or to prevent entirely.

"to treat" means to inhibit or block at least one symptom that characterizes a pathologic condition, in a mammal threatened by, or afflicted with, the condition.

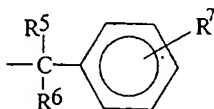
## Compounds of the Invention

Compounds of the invention include quinazolines having the formula:



where:

$R^a$  is iodo;  $(C_1-C_4)$ hydroxyalkyl, methylenedioxy, ethylenedioxy, benzyloxy,  $OCF_3$ ,  $SCF_3$ ,  $SO_3H$ ,  $SO_2F$ ,  $SO_2NR^2R^3$  in which  $R^2$  is hydrogen or  $(C_1-C_4)$ alkyl and  $R^3$  is hydrogen,  $(C_1-C_4)$ alkyl, or phenyl,  $NR^2R^4$  in which  $R^2$  is as defined above and  $R^4$  is phenyl, or  $R^a$  a group of the formula



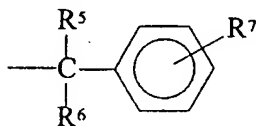
in which  $R^5$  and  $R^6$  are each, independently, hydrogen,  $(C_1-C_4)$ alkyl, or  $(C_1-C_4)$ perfluoroalkyl, and  $R^7$  is hydrogen, halo, hydroxy,  $(C_1-C_4)$ alkyl,  $(C_1-C_3)$ alkoxy,  $(C_1-C_4)$ hydroxyalkyl, or  $N(R^2)_2$  in which  $R^2$  is as defined above;

$n$  is an integer of 1-4;

- $R^b$  is each, independently, hydrogen; halo; hydroxy; mercapto;  $(C_1-C_4)$ alkyl,  $(C_1-C_4)$ alkoxy,  $(C_1-C_4)$ thioalkyl,  $(C_1-C_4)$ hydroxyalkyl, nitro, cyano, methylenedioxy, ethylenedioxy,  $COCH_3$ ,  $CF_3$ ,  $OCF_3$ ,  $SCF_3$ ,  $COOH$ ,  $SO_3H$ ,  $SO_2F$ ; phenyl or phenyl substituted by a group selected from halo, hydroxy, mercapto,  $(C_1-C_4)$ alkyl,  $(C_1-C_4)$ alkoxy,  $(C_1-C_4)$ thioalkyl,  $(C_1-C_4)$ hydroxyalkyl, amino, nitro, cyano,  $CF_3$ ,  $COOH$ ,  $SO_3H$ ,  $SO_2NR^2R^3$  in which  $R^2$  and  $R^3$  are as defined below, and  $SO_2F$ .  $R^a$  can also be benzyloxy or benzyloxy substituted on the phenyl portion by a group defined above,  $NR^2R^3$  in which  $R^2$  is H or  $(C_1-C_4)$ alkyl and  $R^3$  is H,  $(C_1-C_4)$ alkyl, phenyl or phenyl substituted by a group as defined above;
- $R^1$  is  $(C_1-C_4)$ alkyl, preferably methyl, or a pharmaceutically acceptable salt thereof, such as an acid addition salt.

- Preferably,  $R^a$  is a member selected from the group consisting of I,  $NHC_6H_5$ ,  $-OCH_2CH_2O-$ ,  $-OCH_2O-$ ,  $OCF_3$ ,  $SCF_3$ ,  $CH_2OH$ ,  $C_2H_4OH$ ,  $SO_3H$ ,  $SO_2NH_2$ , and  $SO_2F$ ; and more preferably  $R^a$  is I,  $OCF_3$  or  $SO_2F$ . Most preferably,  $R^a$  is I or  $R^a$  is  $OCF_3$ .

In an alternative preferred compound, n is 1 and  $R^a$  is a group of the formula:



- Preferably,  $R^5$  and  $R^6$  are each, independently, H,  $CH_3$  or  $CF_3$ , and most preferably,  $R^5$  and  $R^6$  are  $CF_3$  and  $R^7$  is  $NH_2$ .

- In another preferred compound,  $R^b$  is at least one member selected from the group consisting of F, Cl, Br, I, OH,  $NH_2$ ,  $NO_2$ , CN,  $COOH$ ,  $CH_3$ , and  $CF_3$ , and more preferably  $R^b$  is at least one member selected from the group consisting of F, Cl, Br, OH, and  $CF_3$ .

Additional preferred quinazoline compounds useful in the treatment of tumors are described more fully below and particularly in the Examples. These include:

- 4-(3',5'-dibromo-4'-methylphenyl)amino-6,7-dimethoxyquinazoline;
- 4-(2',4',6'-tribromophenyl)amino-6,7-dimethoxyquinazoline;
- 4-(2',3',5',6'-tetrafluoro-5'-bromophenyl)amino-6,7-dimethoxyquinazoline;

4-(4'-fluorophenyl)amino-6,7-dimethoxyquinazoline;  
4-(4'-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline; and  
4-(3',5'-bis-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline.

## 5 Methods of Treatment

The compounds of the invention are useful for the treatment of animals, including humans. In particular, the compounds of the invention have been found to be potent inhibitors of tumor cell proliferation and survival, and effective to induce apoptosis of malignant cells.

10 Compounds of the invention have surprisingly been found to be effective for inducing apoptosis and/or cytotoxicity of leukemia cells. In particular, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline compounds of the invention have been found to effectively induce apoptosis in multi-drug resistant leukemia. A preferred compound for the treatment of multi-drug resistant leukemia is 4-(3'-  
15 bromo-4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline.

Compounds of the invention that are particularly useful for treating leukemia include:

4-(3',5'-dibromo-4'-methylphenyl)amino-6,7-dimethoxyquinazoline,  
4-(2',4',6'-tribromophenyl)amino-6,7-dimethoxyquinazoline,  
20 4-(2',3',5',6'-tetrafluoro-4'-bromophenyl)amino-6,7-dimethoxyquinazoline,  
4-(4'-fluorophenyl)amino-6,7-dimethoxyquinazoline,  
4-(3'-fluorophenyl)amino-6,7-dimethoxyquinazoline,  
4-(2'-fluorophenyl)amino-6,7-dimethoxyquinazoline,  
25 4-(4'-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline.  
4-(2'-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline, and  
4-(3',5'-bis-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline.

Compounds of the invention that are particularly useful for treating breast tumors  
30 include:

4-(3'-bromophenyl)amino-6,7-dimethoxyquinazoline,  
4-(3',5'-dibromo-4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline.  
4-(3'-chloro-4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline,  
4-(3',5'-bis-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline,



- 4-(2',3',5',6'-tetrafluoro-4'-bromophenyl)amino-6,7-  
dimethoxyquinazoline,  
4-(4'-fluorophenyl)amino-6,7-dimethoxyquinazoline,  
4-(3'-fluorophenyl)amino-6,7-dimethoxyquinazoline, and  
5 4-(2'-fluorophenyl)amino-6,7-dimethoxyquinazoline.

### Compositions

The compounds of the invention are useful as pharmaceutical compositions prepared with a therapeutically effective amount of a compound of claim 1 and a  
10 pharmaceutically acceptable carrier or diluent.

The quinazoline compounds of the invention can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous  
15 routes.

Thus, quinazoline compounds of the invention may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier, or by inhalation or insufflation. They may be enclosed in hard or soft shell gelatin capsules, may be  
20 compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the quinazoline compounds may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The quinazoline compounds may be combined with a fine inert powdered carrier and  
25 inhaled by the subject or insufflated. Such compositions and preparations should contain at least 0.1% quinazoline compounds. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of quinazoline compounds in such therapeutically useful compositions is such that an effective  
30 dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a  
35 sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent

such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the quinazoline compounds may be incorporated into sustained-release preparations and devices.

The quinazoline compounds may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the quinazoline compounds can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the quinazoline compounds which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the

compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the quinazoline compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the quinazoline compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Other solid carriers include nontoxic polymeric nanoparticles or microparticles. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the quinazoline compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the quinazoline compounds to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

Generally, the concentration of the quinazoline compounds in a liquid composition, such as a lotion, will be from about 0.1–25 wt-%, preferably from about 0.5–10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1–5 wt-%, preferably about 0.5–2.5 wt-%.

5           The amount of the quinazoline compounds required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

10           In general, however, a suitable dose will be in the range of from about 0.5 to about 100 mg/kg, e.g., from about 10 to about 75 mg/kg of body weight per day, such as 3 to about 50 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day.

15           The quinazoline compounds are conveniently administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form.

          Ideally, the quinazoline compounds should be administered to achieve peak plasma concentrations of from about 0.5 to about 75  $\mu$ M, preferably, about 1 to 50  $\mu$ M, most preferably, about 2 to about 30  $\mu$ M. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the quinazoline compounds, optionally in saline, or orally administered as a bolus containing about 1–100 mg of the quinazoline compounds. Desirable blood levels may be maintained by continuous infusion to provide about 0.01–5.0 mg/kg/hr or by intermittent infusions  
20           containing about 0.4–15 mg/kg of the quinazoline compounds.

          The quinazoline compounds may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple  
30           inhalations from an insufflator or by application of a plurality of drops into the eye.

#### **Targeting quinazolines to cells**

          In a preferred embodiment, the quinazoline compound is targeted to cells where treatment is desired, for example, to leukemia cells, to breast cells, or to other  
35           tumor cells. The compound is targeted to the desired cell by conjugation to a

targeting moiety that specifically binds the desired cell, thereby directing administration of a conjugated molecule. Useful targeting moieties are ligands which specifically bind cell antigens or cell surface ligands, for example, antibodies against the B cell antigen, CD19 (such as B43) and the like.

5 To form the conjugates of the invention, targeting moieties are covalently bonded to sites on the quinazoline compound. The targeting moiety, which is often a polypeptide molecule, is bound to compounds of the invention at reactive sites, including NH<sub>2</sub>, SH, CHO, COOH, and the like. Specific linking agents are used to join the compounds. Preferred linking agents are chosen according to the reactive  
10 site to which the targeting moiety is to be attached.

Methods for selecting an appropriate linking agent and reactive site for attachment of the targeting moiety to the compound of the invention are known, and are described, for example, in Hermanson, et al., *Bioconjugate Techniques*, Academic Press, 1996; Hermanson, et al., *Immobilized Affinity Ligand Techniques*,  
15 Academic Press, 1992; and *Pierce Catalog and Handbook*, 1996, pp. T155–T201.

#### Administration of quinazolines

According to the invention, quinazoline compounds may be administered prophylactically, i.e., prior to onset the pathological condition, or the  
20 quinazoline compounds may be administered after onset of the reaction, or at both times.

### EXAMPLES

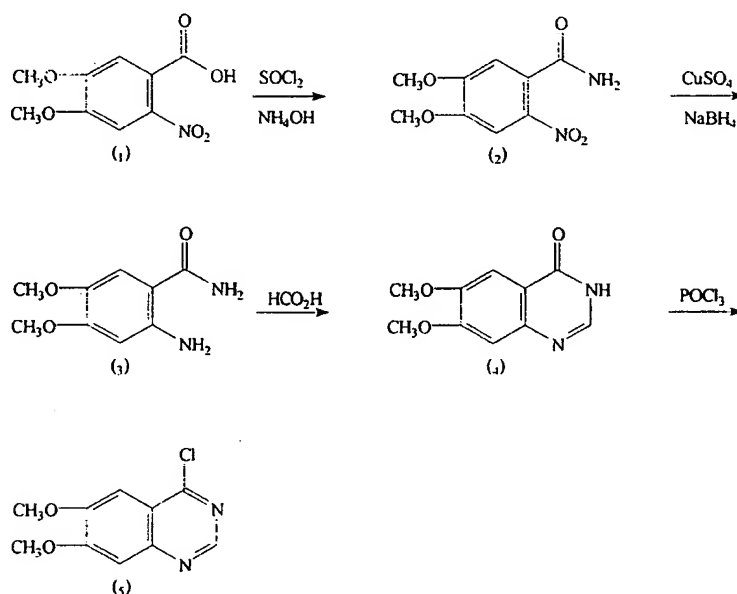
The invention may be further clarified by reference to the following  
25 Examples, which serve to exemplify some of the preferred embodiments, and not to limit the invention in any way.

#### Example 1 Synthesis of Quinazoline Derivatives

30 All chemicals were purchased from the Aldrich Chemical Company, Milwaukee, Wisconsin, and were used directly for synthesis. Anhydrous solvents such as acetonitrile, methanol, ethanol, ethyl acetate, tetrahydrofuran, chloroform, and methylene chloride were obtained from Aldrich as sure seal bottles under  
35 nitrogen and were transferred to reaction vessels by cannulation. All reactions were carried out under a nitrogen atmosphere.

The key starting material, 4-chloro-6,7-dimethoxyquinazoline, was prepared according to published procedures (Nomoto, et al., 1990, *Chem. Pharm. Bull.*, 38:1591-1595; Thomas, C. L., 1970, IN: *Catalytic Processes and Proven Catalysts*, Academic Press, New York, NY) as outlined below in Scheme 1.

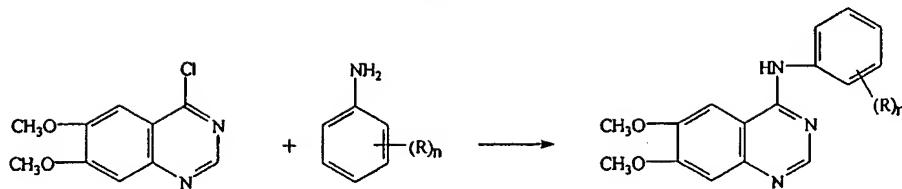
- 5 Specifically, 4,5-dimethoxy-2-nitrobenzoic acid (compound 1) was treated with thionyl chloride to form acid chloride, followed by reacting with ammonia to yield 4,5-dimethoxy-2-nitrobenzamide (compound 2). Compound 2 was reduced with sodium borohydride in the presence of catalytic amounts of copper sulphate to give 4,5-dimethoxy-2-aminobenzamide (compound 3), which was directly refluxed with  
10 formic acid to yield 6,7-dimethoxyquinazoline-4(3H)-one (compound 4). Compound 4 was refluxed with phosphorus oxytrichloride to give 4-chloro-6,7-dimethoxyquinazoline (compound 5) in good yield.



Scheme 1

Substituted quinazoline derivatives were prepared by the condensation of 4-chloro-6,7-dimethoxyquinazoline with substituted anilines as outlined below in Scheme 2:

13



R = substituent; n = number

Scheme 2

5 Specifically, a mixture of 4-chloro-6,7-dimethoxyquinazoline (448 mg, 2 mmols) and the substituted aniline (2.5 mmols) in EtOH (20 ml) was heated to reflux. After refluxing for 4-24 hours, an excess amount of Et<sub>3</sub>N was added, and the solvent was concentrated to give the crude product which was recrystallized from DMF.

10 As discussed above, the novel hydroxy-substituted quinazoline derivatives of the invention were created by reacting the appropriate substituted anilines with the key starting material, 4-chloro-6,7-dimethoxyquinazoline.

#### Physical Characteristics:

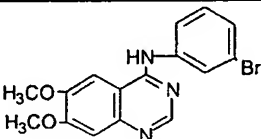
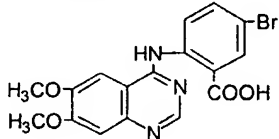
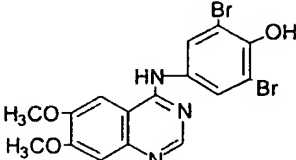
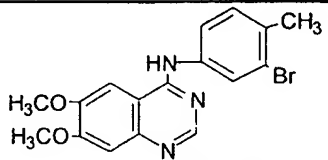
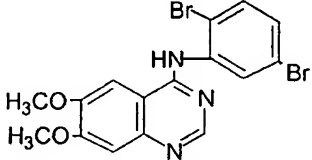
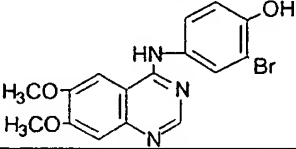
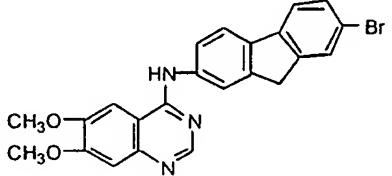
15 Melting points are uncorrected. <sup>1</sup>H NMR spectra were recorded using a Varian Mercury 300 spectrometer in DMSO-d<sub>6</sub> or CDCl<sub>3</sub>. Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard at zero ppm. Coupling constants (J) are given in hertz and the abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet and multiplet, respectively. Infrared spectra were recorded on a Nicolet PROTEGE 460-IR spectrometer. Mass spectroscopy data were recorded on a FINNIGAN MAT 95, VG 7070E-HF G.C. system with an HP 5973 Mass Selection Detector. UV spectra were recorded on BECKMAN DU 7400 and using MeOH as the solvent. TLC was performed on a precoated silica gel plate (Silica Gel KGF; Whitman Inc). Silica gel 25 (200-400 mesh, Whitman Inc.) was used for all column chromatography separations. All chemicals were reagent grade and were purchased from Aldrich Chemical Company (Milwaukee, Wis) or Sigma Chemical Company (St. Louis, MO).

30

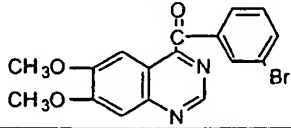
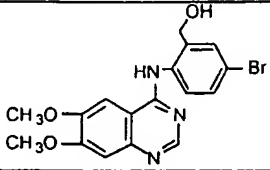
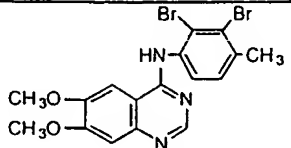
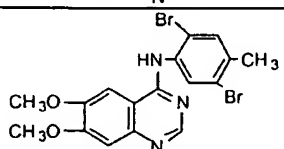
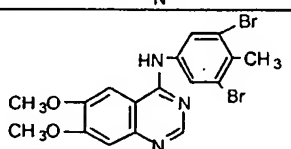
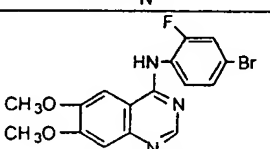
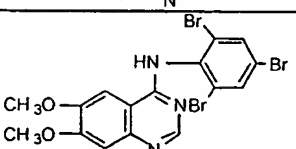
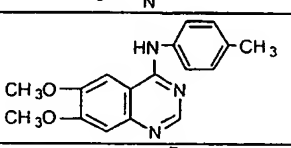
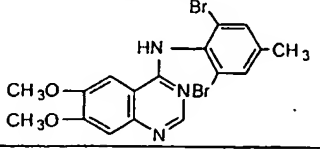
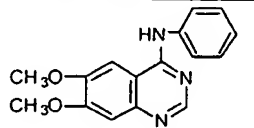
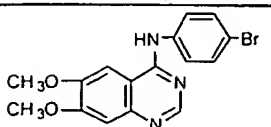
**Example 2****Bromine Substituted Quinazoline Compounds**

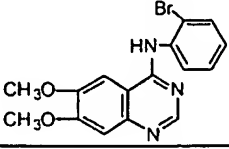
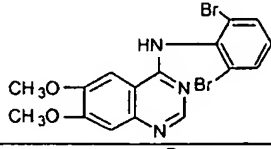
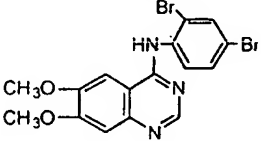
- Bromine substituted quinazoline derivatives were synthesized and characterized as discussed above in Example 1. The structures and physical data are shown below:

**Bromine Substituted Quinazoline Compounds**

No	Name	Structure	Formula	MW
1	P-79		$C_{16}H_{14}BrN_3O_2$	360
2	P-88		$C_{17}H_{14}BrN_3O_4$	404
3	P-97		$C_{16}H_{13}Br_2N_3O_3$	455
4	P-111		$C_{17}H_{16}BrN_3O_2$	374
5	P-112		$C_{16}H_{13}Br_2N_3O_2$	439
6	P-154		$C_{16}H_{14}BrN_3O_3$	376
7	P-160		$C_{23}H_{18}BrN_3O_2$	448



No	Name	Structure	Formula	MW
8	P-164		$C_{17}H_{13}BrN_2O_3$	373
9	P-190		$C_{17}H_{16}BrN_3O_3$	389
10	P-210		$C_{17}H_{15}Br_2N_3O_2$	453
11	P-211		$C_{17}H_{15}Br_2N_3O_2$	453
12	P-212		$C_{17}H_{15}Br_2N_3O_2$	453
13	P-214		$C_{16}H_{13}BrFN_3O_2$	378
14	P-222		$C_{16}H_{12}Br_3N_3O_2$	518
15	P-234		$C_{17}H_{17}N_3O_2$	295
16	P-241		$C_{17}H_{15}Br_2N_3O_2$	453
17	P-258		$C_{16}H_{15}N_3O_2$	281
18	P-260		$C_{16}H_{14}BrN_3O_2$	360

No	Name	Structure	Formula	MW
19	P-261		$C_{16}H_{14}BrN_3O_2$	360
20	P-262		$C_{16}H_{13}Br_2N_3O_2$	439
21	P-263		$C_{16}H_{13}Br_2N_3O_2$	439

**4-(3'-Bromophenyl)-amino-6,7-dimethoxyquinazoline (HI-P79)**

Yield 84.17%; m.p. 246.0–249.0 °C.  $^1H$  NMR(DMSO- $d_6$ ):  $\delta$  10.42(br, s, 1H, NH), 8.68(s, 1H, 2-H), 8.07–7.36(m, 5H, 5, 2', 4', 5', 6'-H), 7.24(s, 1H, 8H), 3.98(s, 3H, -OCH<sub>3</sub>), 3.73(s, 3H, -OCH<sub>3</sub>); IR(KBr) $\nu_{max}$ : 3409, 2836, 1632, 1512, 1443, 1243, 1068  $cm^{-1}$ ; GC/MS  $m/z$  361( $M^+ + 1$ , 61.8), 360( $M^+$ , 100.0), 359( $M^+ - 1$ , 63.5), 344(11.3), 222(10.9), 140(13.7). Anal. ( $C_{16}H_{14}BrN_3O_2$  HCl) C, H, N.

**4-(4'-Bromo-2'-carboxylphenyl)-amino-6,7-dimethoxyquinazoline (HI-P88)**

Yield 92.82 %; m.p. > 300.0 °C.  $^1H$  NMR(DMSO- $d_6$  + CF<sub>3</sub>CO<sub>2</sub>H):  $\delta$  9.95(d, 1H), 8.74(d, 1H, Ar-H), 8.30, 8.28(2d, 2H), 7.95(d, 1H), 7.83(s, 1H), 4.21(s, 3H, -OCH<sub>3</sub>), 4.15(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 205, 229.0 nm. IR(KBr) $\nu_{max}$ : 3444(br), 2737, 1592, 1504, 1443, 1273, 1070  $cm^{-1}$ . GC/MS  $m/z$  388( $M^+ + 1 - OH$ , 18.08), 387( $M^+ - OH$ , 100.00), 386( $M^+ - 1 - OH$ , 30.84), 385(97.52), 299(4.78). Anal. ( $C_{16}H_{14}BrN_3O_2$  HCl) C, H, N.

**4-(3',5'-Dibromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (HI-P97).**

Yield 72.80%; m.p. > 300.0 °C.  $^1H$  NMR(DMSO- $d_6$ ):  $\delta$  9.71(s, 1H, -NH), 9.39(s, 1H, -OH), 8.48(s, 1H, 2-H), 8.07(s, 2H, 2', 6'-H), 7.76(s, 1H, 5-H), 7.17(s, 1H, 8-H), 3.94(s, 3H, -OCH<sub>3</sub>), 3.91(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 208.0, 210.0, 245.0, 320.0 nm; IR(KBr) $\nu_{max}$ : 3504(br), 3419, 2868, 1627, 1512, 1425, 1250, 1155  $cm^{-1}$ ; GC/MS  $m/z$  456( $M^+ + 1$ , 54.40), 455( $M^+$ , 100.00), 454( $M^+ - 1$ , 78.01), 439( $M^+ - OH$ ,

7.96), 376( $M^+ + 1 - \text{Br}$ , 9.76), 375( $M^+ - \text{Br}$ , 10.91), 360(5.23). Anal. ( $\text{C}_{16}\text{H}_{13}\text{Br}_2\text{N}_3\text{O}_3$ ) C, H, N.

**4-(3'-Bromo-4'-methylphenyl)-amino-6,7-dimethoxyquinazoline (HI-P111):**

5 Yield 82.22 %; m.p. 225.0–228 °C.  $^1\text{H}$  NMR(DMSO- $d_6$ ):  $\delta$  10.23(s, 1H, -NH), 8.62(s, 1H, 2-H), 8.06(d, 1H,  $J_{2',6'} = 2.1$  Hz, 2'-H), 7.89(s, 1H, 5-H), 7.71(dd, 1H,  $J_{5',6'} = 8.7$  Hz,  $J_{2',6'} = 2.1$  Hz, 6'-H), 7.37(d, 1H,  $J_{5',6'} = 8.7$  Hz, 5'-H), 7.21(s, 1H, 8-H), 3.96(s, 3H, -OCH<sub>3</sub>), 3.93(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 204.0, 228.0, 255.0, 320.0 nm. IR(KBr) $\nu_{\text{max}}$ : 3431, 3248, 2835, 1633, 1517, 1441, 1281, 1155  $\text{cm}^{-1}$ .  
 10 GC/MS  $m/z$  375( $M^+ + 1$ , 76.76), 374( $M^+$ , 100.00), 373( $M^+ - 1$ , 76.91), 358( $M^+ + 1 - \text{OH}$ , 11.15), 357(1.42), 356(6.31). Anal. ( $\text{C}_{17}\text{H}_{16}\text{BrN}_3\text{O}_2 \cdot \text{HCl}$ ) C, H, N.

**4-(2',5'-Dibromophenyl)-amino-6,7-dimethoxyquinazoline (HI-P112):**

Yield 70.05%; m.p. >300.0 °C.  $^1\text{H}$  NMR(DMSO- $d_6$ ):  $\delta$  11.51(s, 1H, -NH), 8.76(s, 1H, 2-H), 8.21(s, 1H, 5-H), 7.81(d, 1H,  $J_{4',6'} = 2.4$  Hz, 6'-H), 7.75(d, 1H,  $J_{3',4'} = 8.7$  Hz, 3'-H), 7.55(dd, 1H,  $J_{4',6'} = 2.4$  Hz,  $J_{3',4'} = 8.7$  Hz, 4'-H), 7.33(s, 1H, 8-H), 3.98(s, 3H, -OCH<sub>3</sub>), 3.97(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 208.0, 238.0, 330.0 nm. IR(KBr) $\nu_{\text{max}}$ : 3444, 2836, 1628, 1510, 1431, 1277, 1070  $\text{cm}^{-1}$ . GC/MS  $m/z$  440( $M^+ + 1$ , 10.12), 439( $M^+$ , 7.0), 438( $M^+ - 1$ , 3.63), 360( $M^+ + 1 - \text{Br}$ , 99.42), 359( $M^+ - \text{Br}$ , 20.45), 358( $M^+ - 1 - \text{Br}$ , 100.00), 343(20.80), 299(8.62). Anal. ( $\text{C}_{16}\text{H}_{13}\text{Br}_2\text{N}_3\text{O}_2 \cdot \text{HCl}$ ) C, H, N.  
 20

**4-[(3'-Bromo-9'-fluorenone)-2'-lamino]-6,7-dimethoxyquinazoline (HI-P119):**

25 Yield 75.23%; m.p. 255.0–257.0 °C.  $^1\text{H}$  NMR(DMSO- $d_6$ ):  $\delta$  8.77(s, 1H, -NH), 8.33(s, 1H, 2-H), 7.89(s, 1H, 5-H), 7.40(s, 1H, 8-H), 7.74–7.26(m, 6H, Ar-H), 4.12(s, 3H, -OCH<sub>3</sub>), 4.11(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 205, 229.0, 251.0, 320.0 nm. IR(KBr) $\nu_{\text{max}}$ : 3444, 2836, 1628, 1510, 1431, 1277, 1070  $\text{cm}^{-1}$ . GC/MS  $m/z$  464( $M^+ + 2$ , 40.81), 463( $M^+ + 1$ , 7.56), 462( $M^+$ , 27.26), 384( $M^+ + 2 - \text{Br}$ , 69.56), 383( $M^+ + 1 - \text{Br}$ , 35.50), 382( $M^+ - \text{Br}$ , 100.00), 352(10.85), 206(26.73), 191(11.31). Anal. ( $\text{C}_{23}\text{H}_{16}\text{BrN}_3\text{O}_3 \cdot \text{HCl}$ ) C, H, N.  
 30

**4-(2',3',5'.6'-Tetrafluoro-4'-bromophenyl)-amino-6,7-dimethoxyquinazoline (HI-P144):**

Yield 78.24%; m.p. 180.0–182.0°C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 7.78(s, 1H, 2-H), 7.53(s, 1H, 5-H), 6.79(s, 1H, 8-H), 3.81(s, 3H, -OCH<sub>3</sub>), 3.3.79(s, 3H, -OCH<sub>3</sub>).

5 Anal (C<sub>16</sub>H<sub>10</sub> BrF<sub>4</sub>N<sub>3</sub>O<sub>2</sub>.HCl) C, H, N.

**4-(3'-Bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline (HI-P154):**

Yield 89.90%; m.p. 233.0–233.5 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 10.08(s, 1H, -NH), 9.38(s, 1H, -OH), 8.40(s, 1H, 2-H), 7.89(d, 1H, *J*<sub>2',6'</sub> = 2.7 Hz, 2'-H), 7.75(s, 1H, 5-H), 7.55(dd, 1H, *J*<sub>5',6'</sub> = 9.0 Hz, *J*<sub>2',6'</sub> = 2.7 Hz, 6'-H), 7.14(s, 1H, 8-H), 6.97(d, 1H, *J*<sub>5',6'</sub> = 9.0 Hz, 5'-H), 3.92(s, 3H, -OCH<sub>3</sub>), 3.90(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 203.0, 222.0, 250.0, 335.0 nm. IR(KBr)<sub>ν</sub><sub>max</sub>: 3431(br), 2841, 1624, 1498, 1423, 1244 cm<sup>-1</sup>. GC/MS *m/z* 378(M<sup>+</sup> +2, 90.68), 377(M<sup>+</sup> +1, 37.49), 376(M<sup>+</sup>, 100.00), 360(M<sup>+</sup>, 3.63), 298(18.86), 282 (6.65). Anal. (C<sub>16</sub>H<sub>14</sub>BrN<sub>3</sub>O<sub>3</sub>.HCl) C, H, N.

**4-[(7'-Bromofluorene)-2']-amino-6,7-dimethoxyquinazoline (HI-P160):**

Yield 73.21 %; m.p. 254.0–256.0 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 9.69(br, s, 1H, -NH), 8.52(s, 1H, 2-H), 8.12–7.20(m, 9H, 5, 8, 1', 3', 4', 5', 6', 8', 9'-H), 3.99(s, 3H, -OCH<sub>3</sub>), 3.94(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 208.0, 223.0, 348.0 nm. IR(KBr)<sub>ν</sub><sub>max</sub>: 3421, 2820, 1624, 1516, 1431, 1294, 1223 cm<sup>-1</sup>. GC/MS *m/z* 450(M<sup>+</sup> +2, 100), 449(M<sup>+</sup> +1, 35), 448(M<sup>+</sup>, 95), 311(25). Anal. (C<sub>23</sub>H<sub>18</sub>BrN<sub>3</sub>O<sub>2</sub>.HCl) C, H, N.

**4-(3'-Bromobenzoyl)-6,7-dimethoxyquinazoline (HI-P164):**

Yield 81.20%, m.p. 258.0–263.0 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 9.25(s, 1H, 2-H), 8.14(s, 1H, 5-H), 7.92–7.43(m, 4H, 2', 4', 5', 6'-H), 7.40(s, 1H, 8-H), 4.11(s, 3H, -OCH<sub>3</sub>), 4.00(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 203.0, 220.0, 238.0 nm. IR(KBr)<sub>ν</sub><sub>max</sub>: 3432, 1664, 1504, 1431, 1230 cm<sup>-1</sup>. GC/MS *m/z* 374(M<sup>+</sup> +1, 48.96), 373(M<sup>+</sup>, 34.93), 372(M<sup>+</sup> -1, 47.67), 357(58.74), 343(100.00), 293(M<sup>+</sup> -Br, 31.48), 189(26.27). Anal. (C<sub>17</sub>H<sub>13</sub>BrN<sub>2</sub>O<sub>3</sub>) C, H, Br, N.

**4-(4'-Bromo-6'-hydroxymethylphenyl)-amino-6,7-dimethoxyquinazoline  
(HI-P190):**

Yield 73.08 %; m.p. 222.0–223.0 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.30(s, 1H, -OH), 8.22(s, 1H, -NH), 7.77–7.23(m, 5H, 5, 8, 2', 3', 5'-H), 4.49(s, 2H, PhCH<sub>2</sub>-H), 4.01(s, 3H, -OCH<sub>3</sub>), 3.90(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 207.0, 250.0, 332.0 nm.  
IR(KBr)ν<sub>max</sub>: 3446, 2829, 2752, 1652, 1560, 1471, 1365, 1280 cm<sup>-1</sup>. GC/MS m/z 391(M<sup>+</sup>+1, 29.33), 389(M<sup>+</sup>, 29.82), 360(M<sup>+</sup>-CH<sub>2</sub>OH, 50.76), 358(52.39), 311(18.33), 280(43.20), 206(62.80), 191(100.00). Anal. (C<sub>17</sub>H<sub>16</sub>BrN<sub>3</sub>O<sub>3</sub>·HCl) C, H, N.

10

**4-(2',3'-Dibromo-4'-methylphenyl)-amino-6,7-dimethoxyquinazoline (HI-P210):**

Yield 81.24%, mp 233.0–236.0 °C, <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 8.55(s, 1H, -NH), 8.08(s, 1H, 2-H), 7.33–7.17(m, 4H, 5, 8, 5', 6'-H), 3.89(s, 6H, -OCH<sub>3</sub>), 2.35(s, 3H, -CH<sub>3</sub>). UV(MeOH): 207.0, 232.0, 247.0, 330.0 nm. IR ν<sub>max</sub> (KBr) : 3448, 2840, 1629, 1580, 1525, 1420, 1281 cm<sup>-1</sup>. GC/MS m/z 454(M<sup>+</sup>+1, 4.45), 453(M<sup>+</sup>, 11.31), 452(M<sup>+</sup>-1, 4.45), 375(20.36), 374(97.59), 373(23.55), 372(100.00), 358(19.61), 356(18.43). Anal. (C<sub>17</sub>H<sub>15</sub>Br<sub>2</sub>N<sub>3</sub>O<sub>2</sub>·HCl) C, H, N.

**4-(2',5'-Dibromo-4'-methylphenyl)-amino-6,7-dimethoxyquinazoline (HI-P211):**

Yield 83.50 %; m.p. 282.0–284.0°C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>) : δ 11.30(s, 1H, -NH), 8.58(s, 1H, 2-H), 8.00(s, 1H, 5-H), 7.65(s, 1H, 6'-H), 7.60(s, 1H, 3'-H), 7.13(s, 1H, 8-H), 3.79(s, 3H, -OCH<sub>3</sub>), 3.78(s, 3H, -OCH<sub>3</sub>), 2.29(s, 3H, -CH<sub>3</sub>). UV(MeOH): 207.0, 239.0, 330.0 nm. IR(KBr)ν<sub>max</sub>: 3442, 2620, 1631, 1580, 1514, 1380, 1280 cm<sup>-1</sup>. GC/MS m/z 454(M<sup>+</sup>+1, 5.86), 453(M<sup>+</sup>, 16.16), 452(M<sup>+</sup>-1, 5.35), 374(92.12), 373(23.66), 372(100.00), 358(17.68), 356(17.35). Anal. (C<sub>17</sub>H<sub>15</sub>Br<sub>2</sub>N<sub>3</sub>O<sub>2</sub>·HCl) C, H, N.

**4-(3',5'-Dibromo-4'-methylphenyl)-amino-6,7-dimethoxyquinazoline (HI-P212):**

Yield 83.47 %; m.p. 275.0–279.0°C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.30(s, 1H, -NH), 8.58(s, 1H, 2-H), 8.35(s, 1H, 5-H), 7.24(s, 2H, 2', 6'-H), 7.13(s, 1H, 8-H), 3.91(s, 3H, -OCH<sub>3</sub>), 3.88(s, 3H, -OCH<sub>3</sub>), 2.31(s, 3H, -CH<sub>3</sub>). UV(MeOH): 237.0, 307.0.

319.0 nm. IR(KBr) $\nu_{\max}$ : 3471, 3434, 2640, 1633, 1580, 1504, 1420, 1281  $\text{cm}^{-1}$ .  
 GC/MS  $m/z$  454( $M^+ + 1$ , 5.34), 453( $M^+$ , 16.05), 452( $M^+ - 1$ , 5.87), 374(99.02),  
 373(26.20), 372(100.00), 358(20.39), 356(19.98), 32(8.29), 314(8.49), 206(19.02).  
 Anal. ( $\text{C}_{17}\text{H}_{15}\text{Br}_2\text{N}_3\text{O}_2 \text{HCl}$ ) C, H, N.

5

**4-(2'-Fluoro-4'-bromophenyl)-amino-6,7-dimethoxyquinazoline (HI-P214):**

Yield 77.21 %; m.p. 243.0–245.0°C.  $^1\text{H}$  NMR(DMSO- $d_6$ ):  $\delta$  8.57(s, 1H, 2-H),  
 7.91(s, 1H, 5-H), 7.57(d, 1H, 3'-H), 7.34 (m, 2H, 5', 6'-H), 7.07(s, 1H, 8-H), 3.78(s,  
 3H,  $-\text{OCH}_3$ ), 3.77(s, 3H,  $-\text{OCH}_3$ ). UV(MeOH): 204.0, 215.0, 250.0, 330.0 nm.

10 IR(KBr) $\nu_{\max}$ : 3431, 2629, 1633, 1580, 1511, 1420, 1278  $\text{cm}^{-1}$ . GC/MS  $m/z$   
 379( $M^+ + 1$ , 34.39), 378( $M^+$ , 21.33), 377( $M^+ - 1$ , 39.08), 360(62.05), 359(31.58),  
 358(62.57), 357(19.81), 299(19.31), 298(100.00), 282(17.88), 240(28.76). Anal.  
 ( $\text{C}_{16}\text{H}_{13}\text{BrFN}_3\text{O}_2 \text{HCl}$ ) C, H, N.

15 **4-(2',4',6'-Tribromophenyl)amino-6,7-dimethoxyquinazoline (HI-P222):**

Yield 54.86 %; m.p. 250.0–255.0 °C.  $^1\text{H}$  NMR(DMSO- $d_6$ ):  $\delta$  8.00(s, 1H, 2-H),  
 7.89(s, 2H, 3', 5'-H), 7.74(s, 1H, 5-H), 7.01(s, 1H, 8-H), 3.87(s, 3H,  $-\text{OCH}_3$ ),  
 3.86(s, 3H,  $-\text{OCH}_3$ ). UV(MeOH): 209.0, 236.0, 333.0 nm. IR(KBr) $\nu_{\max}$ : 3417, 2838,  
 1625, 1514, 1429, 1276, 1073  $\text{cm}^{-1}$ . GC/MS  $m/z$  519( $M^+ + 1$ , 18.12), 518( $M^+$ , 17.30),  
 20 517( $M^+ - 1$ , 16.63), 439( $M^+ + 1 - \text{Br}$ , 99.42), 438( $M^+ - \text{Br}$ , 95.45), 437( $M^+ - 1 - \text{Br}$ ,  
 100.00), 359(20.80), 358(18.62), 357(19.32), 281(88.98), 207(15.42). Anal.  
 ( $\text{C}_{16}\text{H}_{12}\text{Br}_3\text{N}_3\text{O}_2 \text{HCl}$ ) C, H, N.

25 **4-(2',6'-Dibromo-4'-methylphenyl)-amino-6,7-dimethoxyquinazoline (HI-P241):**

Yield 79.47 %, m.p. 235.0–237.0 °C.  $^1\text{H}$  NMR(DMSO- $d_6$ ):  $\delta$  9.77(s, 1H,  $-\text{HN}$ ), 8.20  
 (s, 1H, 2-H), 7.87(s, 1H, 8-H), 7.61(s, 2H, 3', 5'-H), 7.15(s, 1H, 5-H), 3.93(s, 6H,  
 $-\text{OCH}_3$ ). UV(MeOH): 208.0, 245.0, 318.0, 339.0 nm. IR(KBr) $\nu_{\max}$ : 3241, 2839,  
 2783, 1635, 1580, 1514, 1420, 1360, 1281  $\text{cm}^{-1}$ . GC/MS  $m/z$  454( $M^+ + 1$ , 7.86),  
 30 453( $M^+$ , 56.16), 452( $M^+ - 1$ , 15.30), 374(95.12), 373(18.66), 372(100.00), 358(29.64),  
 356(19.36). Anal. ( $\text{C}_{17}\text{H}_{15}\text{Br}_2\text{N}_3\text{O}_2 \text{HCl}$ ) C, H, N.

**4-(4'-Bromophenyl)-amino-6,7-dimethoxyquinazoline (HI-P260):**

Yield 75.28%. m.p.270.0-272.0 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>) : δ 11.30(s, 1H, -NH), 8.85(s, 1H, 2-H), 8.27(s, 1H, 5-H), 7.70(s, 4H, 2',3',5',6'-H), 7.32(s, 1H, 8H), 4.02(s,3H, -OCH<sub>3</sub>), 4.00(s,3H, -OCH<sub>3</sub>). UV(MeOH):204.0, 218.0, 252.0, 335.0 nm.  
 5 IR(KBr) ν<sub>max</sub>: 3431, 3034, 2636,1635, 1589,1514. 1435, 1284 cm<sup>-1</sup>. GC/MS m/z 361 ( M<sup>+</sup>+1,74.00) , 360( M<sup>+</sup>, 100.00), 359( M<sup>+</sup>-1,72.00), 358( M<sup>+</sup>-2, 95.00). 329 (3.20 ), 301 ( 13.0 ), 281 ( 21.0 ), 207( 38.0 ). Anal. (C<sub>16</sub>H<sub>14</sub>BrN<sub>3</sub>O<sub>2</sub>.HCl) C, H, N.

**4-(2'-Bromophenyl)-amino-6,7-dimethoxyquinazoline (HI-P261):**

10 Yield 71.94%; m.p.241.0-243.0 °C. <sup>1</sup>H NMR( DMSO-d<sub>6</sub>) : δ 11.67 ( d, 1H, -NH), 8.79 ( s, 1H, 2-H ), 8.32 ( s, 1H, 5-H ), 7.86-7.38 ( m, 4H, 3', 4', 5',6'-H ), 7.40 ( s, 1H, 8H ), 4.01 ( s,6H, -OCH<sub>3</sub> ). UV(MeOH): 204.0, 226.0, 248.0, 330.0 nm.  
 IR(KBr) ν<sub>max</sub>:3454, 3032, 2638,1630, 1589,1514, 1430, 1281 cm<sup>-1</sup>. GC/MS m/z 361(M<sup>+</sup>+1, 7.00) , 360(M<sup>+</sup>, 5.00), 359(M<sup>+</sup>-1,6.00), 358(M<sup>+</sup>-2, 5.00). 301(13.0),  
 15 281(21.0), 280(100.00), 207(25.00). Anal (C<sub>16</sub>H<sub>14</sub>BrN<sub>3</sub>O<sub>2</sub>.HCl) C, H, N.

**4-(2',6'-Dibromophenyl)-amino-6,7-dimethoxyquinazoline (HI-P262):**

Yield 69.45%, mp 243.0-246.0 °C, <sup>1</sup>H NMR( DMSO-d<sub>6</sub>) : δ 11.91(d, 1H, -NH), 8.80(s, 1H, 2-H), 8.43(s, 1H, 5-H), 7.86(d, 2H, J= 8.4 Hz, 3', 5'-H), 7.49(s, 1H, 8H), 7.35(t, 1H, J= 8.4 Hz, 4'-H), 4.02(s,3H, -OCH<sub>3</sub>), 4.01(s,3H, -OCH<sub>3</sub> ).  
 20 UV(MeOH): 208.0, 227.0, 245.0, 330.0 nm. IR(KBr)ν<sub>max</sub>:3454, 3032, 2638.1630, 1589,1514, 1430, 1281 cm<sup>-1</sup>.

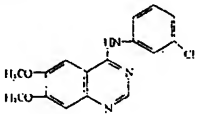
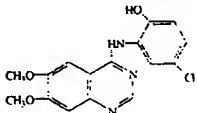
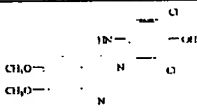
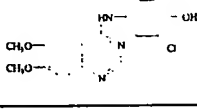
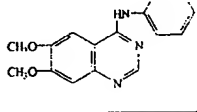
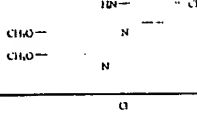
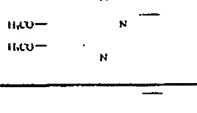
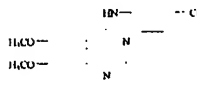
**4-(2',4'-Dibromophenyl)-amino-6,7-dimethoxyquinazoline (HI-P263):**

25 Yield 70.62 %; m.p.257.0- 262.0 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>) : δ 11.91(d, 1H, -NH), 8.79 (s, 1H, 2-H), 8.21(s, 1H, 5-H ), 8.12-7.51(m, 3H, 3',5',6'-H), 7.35(s, 1H, 8-H), 4.01(s,3H, -OCH<sub>3</sub>), 3.99(s, 3H, -OCH<sub>3</sub>). UV(MeOH):208.0, 210.0, 248.0, 330.0 nm. IR(KBr) ν<sub>max</sub>: 3458, 3028, 2641, 1633, 1594, 1511. 1435, 1277 cm<sup>-1</sup>.

## Example 3

Chlorine Substituted Quinazoline Compounds

- 5 Chlorine substituted quinazoline derivatives were synthesized and characterized as discussed above in Example 1. The structures and physical data are shown below:

No	Name	Structure	Formula	MW
1	P-87		$C_{16}H_{14}ClN_3O_2$	316
2	P-93		$C_{16}H_{14}ClN_3O_3$	331
3	P-189		$C_{16}H_{13}Cl_2N_3O_3$	365
4	P-197		$C_{16}H_{14}ClN_3O_3$	331
5	P-268		$C_{16}H_{14}ClN_3O_2$	316
6	P-269		$C_{16}H_{14}ClN_3O_2$	316
7	P-278		$C_{16}H_{14}ClN_3O_3$	331
8	P-415		$C_{20}H_{16}ClN_3O_2$	365

- 10 *4-(3'-Chlorophenyl)-amino-6,7-dimethoxyquinazoline(HI-P87).*

Yield 76.98%; m.p. 242.0–245.0°C.  $^1H$  NMR(DMSO- $d_6$  :  $\delta$  10.47(br, s, 1H, NH), 8.69(s, 1H, 2-H), 8.06(s, 1H, 5-H), 7.95–7.23(m, 4H, 2', 4', 5', 6'-H), 7.24(s, 1H, 8-H), 3.98(s, eH,  $-OCH_3$ ), 3.35(s, 3H,  $OOCH_3$ ). UV(MeOH): 228.0, 251.0, 332.0 nm.



IR(KBr) $\nu_{\max}$ : 3406, 2839, 1632, 1516, 1443, 1278, 1068  $\text{cm}^{-1}$ . GC/MS  $m/z$  316( $M^+ - 1$ , 68.34), 314( $M^+ - 2$ , 100.00), 344(11.34), 222(4.35), 140(9.86). Found: C, 54.62; H, 4.68; N, 11.93; Cl, 19.23.  $\text{C}_{16}\text{H}_{14}\text{ClN}_3\text{O}_2 \cdot \text{HCl}$  requires: C, 54.70; H, 4.28; N, 11.96; Cl, 19.96%.

5

**4-(*c'*-Chloro-6'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline(HI-P93)**

Yield 83.08%; m.p. 295.0°C(dec).  $^1\text{H}$  NMR(DMSO- $d_6$ ):  $\delta$  10.14(s, 1H, -OH), 8.37(s, 1H, 2-H), 7.78(s, 1H, 5H), 7.57(d, 1H,  $J_{2,4'}=2.4$  Hz, 2'-H), 7.16(s, 1H, 8-H), 7.07(dd, 1H,  $J_{2,4'}=2.4$  Hz,  $J_{4',5'}=8.7$  Hz, 4'-H), 6.92(d, 1H,  $J_{4',5'}=8.7$  Hz, 5'-H), 3.93(s, 3H, -OCH<sub>3</sub>), 3.92(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 205, 229.0, 251.0, 320.0 nm. IR(KBr) $\nu_{\max}$ : 3500(br), 3430, 2835, 1622, 1512, 1432, 1259  $\text{cm}^{-1}$ . GC/MS  $m/z$  333( $M^+ + 2$ , 13.41), 332( $M^+ + 1$ , 9.73), 331( $M^+$ , 39.47), 314( $M^+ - \text{OH}$ , 100.00), 298(7.64). Found: C, 52.25; H, 4.07; N, 11.39.  $\text{C}_{16}\text{H}_{14}\text{ClN}_3\text{O}_3 \cdot \text{HCl}$  requires: C, 52.32; H, 4.09; N, 11.44%.

15

**4-(4'-Hydroxyl-3',5'-dichlorophenyl)amino-6,7-dimethoxyquinazoline(HI-PI89)**

Yield 79.45%; m.p. 293.0–295.0°C.  $^1\text{H}$  NMR(DMSO- $d_6$ ):  $\delta$  11.32(s, 1H, -NH), 10.34(s, 1H, -OH), 8.87(s, 1H, 2-H), 8.29(s, 1H, 5-H), 7.90(s, 2H, 2', 6'-H), 7.32(s, 1H, 8-H), 4.01(s, 3H, -OCH<sub>3</sub>), 3.99(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 213.0, 232.0, 250.0, 335.0 nm. IR(KBr) $\nu_{\max}$ : 3479, 2564, 1641, 1579, 1429, 1282, 1147  $\text{cm}^{-1}$ . GC/MS  $m/z$  367( $M^+ = 2$ , 66.57), 366( $M^+ = 1$ , 75.91), 365( $M^+$ , 100.00), 364( $M^+ - 1$ , 94.08), 349( $M^+ - \text{OH}$ , 11.16). Anal. ( $\text{C}_{16}\text{H}_{13}\text{Cl}_2\text{N}_3\text{O}_3$ ) C, H, N. Found: C, 48.93; H, 4.51; N, 10.00.  $\text{C}_{17}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_3 \cdot \text{HCl}$  requires: C, 48.80; H, 4.31; N, 10.04. %.

25

**4-(3'-Chloro-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (HI-PI97)**

Yield 84.14%; m.p. 245.0°C(dec).  $^1\text{H}$  NMR(DMSO- $d_6$ ):  $\delta$  10.00(s, 1H, -NH), 9.37(s, 1H, -OH), 8.41(s, 1H, 2-H), 7.78(s, 1H, 5-H), 7.49(d, 1H,  $J_{2,5'}=2.7$  Hz, 2'-H), 7.55(dd, 1H,  $J_{5,6'}=9.0$  Hz,  $J_{2,6'}=2.7$  Hz, 6'-H), 7.16(s, 1H, 8-H), 6.97(d, 1H,  $J_{5,6'}=9.0$  Hz, 5'-H), 3.93(s, 3H, -OCH<sub>3</sub>), 3.91(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 209.0, 224.0, 249.0, 330.0 nm. IR(KBr) $\nu_{\max}$ : 3448, 2842, 1623, 1506, 1423, 1241  $\text{cm}^{-1}$ . GC/MX  $m/z$ : 341 ( $M^+$ , 100.00), 326( $M^+ - \text{CH}_3$ , 98.50), 310( $M^+ - \text{OCH}_3$ , 12.5),

30

295(9.0), 189(13.5), 155(13.8). Found: C, 52.135; H, 4.16; Cl, 19.15; N, 11.39.  
C<sub>16</sub>H<sub>14</sub>ClN<sub>3</sub>O<sub>3</sub>. HCl requires: C, 52.32; H, 4.09; Cl, 19.07; N, 11.44%.

**4-(2'-Chlorophenyl)-amino-6,7-dimethoxyquinazoline (HI-P268)**

5 Yield 87.28%; m.p. 247.0–279.5°C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.71 (s, 1H, –NH), 8.78 (s, 1H, 2-H), 8.33 (s, 1H, 5-H), 7.67 (s, 1H, 8H), 7.68–7.42 (m, 4H, 3',4,5,6'-H), 4.00 (s, 3H –OCH<sub>3</sub>), 3.99(s, 3H, –OCH<sub>3</sub>). UV(MeOH): 213.0, 234.0, 251.0, 331.0 nm. IR(KBr)ν<sub>max</sub>: 3479, 2566, 1643, 1577, 1429, 1282, 1147 cm<sup>-1</sup>. GC/MX m/z 317 (M<sup>+</sup>+1, 6.60), 316(M<sup>+</sup>, 6.60), 315(M<sup>+</sup>-1, 18.52), 314(M<sup>+</sup>-2, 11.11), 281  
10 (21.22), 280 (M<sup>+</sup>-Cl, 100.00), 264 (29.62). Found: C, 54.51; H, 4.41; N, 11.81. C<sub>16</sub>H<sub>14</sub>ClN<sub>3</sub>O<sub>2</sub>. HCl requires: C, 54.45; H, 4.26; N, 11.93%.

**4-(4'-Chlorophenyl)-amino-6,7-dimethoxyquinazoline (HI-P269)**

Yield 94.94%. m.p. 248.0–250.0°C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.62 (s, 1H, –NH),  
15 8.85 (s, 1H, 2-H), 8.42 (s, 1H, 5-H), 7.88 (d, 2H, J=8.7 Hz, 3',5',-H), 7.54 (d, 2H, J=8.7 Hz, 2',6',-H), 7.38 (s, 1H, 8-H), 4.02 (s, 3H, –OCH<sub>3</sub>), 3.99(s, 3H, –OCH<sub>3</sub>). UV(MeOH): 215.0, 230.0, 253.0, nm. IR(KBr)ν<sub>max</sub>: 3477, 2563, 1640, 1578 cm<sup>-1</sup>. GC/MX m/z 317 (M<sup>+</sup>+1, 18.18), 316(M<sup>+</sup>, 29.55), 315 (M<sup>+</sup>-1, 48.85), 314 (M<sup>+</sup>-2, 61.36), 281 (32.,95), 207 (100.00). Found: C, 54.65; H, 4.38; N, 11.92.  
20 C<sub>16</sub>H<sub>14</sub>ClN<sub>3</sub>O<sub>2</sub>. HCl requires: C, 54.55; H, 4.26; N, 11.93%.

**4-(4'-Hydroxyl-2'-chlorophenyl)-amino-6,7-dimethoxy-quinazoline (HI-P278)**

Yield 81.44%; m.p. 245.0–247.0°C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.39(s, 1H, –NH),  
25 10.30(s, 1H, –OH), 8.75(s, 1H, 2-H), 8.24(s, 1H, 5-H), 7.38–6.85(m, 3H, 3',5',6'-H), 7.37(s, 1H, 8H), 3.98(s, 3H, –OCH<sub>3</sub>), 3.96(s, 3H, –OCH<sub>3</sub>). UV(MeOH): 222.0, 234.0, 239.0, 245.0, 254.0, 348.0 nm. IR(KBr)ν<sub>max</sub>: 3448, 3242, 3144, 3025, 2917, 2834, 1638, 1591, 1514, 1437, 1365, 1277, 1209 cm<sup>-1</sup>. GC/MS m/z: 332(M<sup>+</sup>+1, 5.00), 331(M<sup>+</sup>, 17.00), 330(M<sup>+</sup>-1, 5.00), 297(17.00), 296(100.00), 281(18.00),  
30 280(29.00), 253(9.00). Found: C, 52.17; H, 4.06; N, 11.32. C<sub>16</sub>H<sub>14</sub>ClN<sub>3</sub>O<sub>3</sub>. HCl requires: C, 52.32; H, 4.01; N, 11.44%.

**4-(4'-Chloronaphthyl-1')-amino-6,7-dimethoxyquinazoline (HI-P415)**

Yield, 85.07%. m.p. 245.0–248.0°C <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.91(s, 1H, -NH), 8.66(s, 1H, 2-H), 8.45(s, 1H, 5-H), 8.30–7.62(m, 6H, 2', 3', 5', 6', 7', 8'-H), 7.38(s, 1H, 8-H), 4.03(s, 3H, -OCH<sub>3</sub>), 4.01(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 211.0, 233.0, 250.0, mn. IR(KBr)ν<sub>max</sub>: 3481, 2567, 1645, 1579cm<sup>-1</sup>. Found: C, 59.32; H, 4.27; N, 10.24. C<sub>20</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>2</sub>. HCl. requires: C, 59.70; H, 4.23; N, 10.48%.

**Example 4****Iodine Substituted Quinazoline Compounds**

Iodine substituted quinazoline derivatives were synthesized as discussed above in Example 1, and analyzed. The structures and physical data are shown below:

**Iodine Substituted Quinazoline Compounds**

No	Name	Structure	Formula	MW
1	P-270		C <sub>16</sub> H <sub>14</sub> IN <sub>3</sub> O <sub>2</sub>	407
2	P-271		C <sub>16</sub> H <sub>14</sub> IN <sub>3</sub> O <sub>2</sub>	407
3	P-300		C <sub>16</sub> H <sub>14</sub> IN <sub>3</sub> O <sub>2</sub>	407
4	P-294		C <sub>16</sub> H <sub>13</sub> I <sub>2</sub> N <sub>3</sub> O <sub>3</sub>	549
5	P-299		C <sub>16</sub> H <sub>14</sub> IN <sub>3</sub> O <sub>3</sub>	423

**4-(2'-Iodophenyl)-amino-6,7-dimethoxyquinazoline (P-270):**

Yield 75.37%; m.p. 225.0–230.0 °C. <sup>1</sup>H NMR( DMSO-d<sub>6</sub>) : δ 11.74(s, 1H, -NH), 8.79(s, 1H, 2-H), 8.33(s, 1H, 5-H), 8.05–7.13(m, 4H, 3',4,5,6'-H), 7.44(s, 1H, 8H), 4.01(s, 6H, -OCH<sub>3</sub>). UV(MeOH): 219.0, 222.0, 253.0, 342.0 nm..

- 5 IR(KBr)ν<sub>max</sub>: 3165, 3027, 2827, 1639, 1572, 1501, 1434, 1275, 1070 cm<sup>-1</sup>. GC/MS m/z 408(M<sup>+</sup>+1, 3.47), 407(M<sup>+</sup>, 15.28), 406(M<sup>+</sup>-1, 3.47), 281 (33.33), 280(M<sup>+</sup>-I, 100.00), 264(50.00), 207(34.72). Found: C, 43.62; H, 3.60; N, 9.42. C<sub>16</sub>H<sub>14</sub>IN<sub>3</sub>O<sub>2</sub>.HCl requires: C, 43.34; H, 3.38; N, 9.48%.

**4-(3'-Iodophenyl)-amino-6,7-dimethoxyquinazoline (HI-P271):**

Yield 79.85%; m.p. 235.0–242.0 °C. <sup>1</sup>H NMR( DMSO-d<sub>6</sub>) : δ 11.43 ( s, 1H, -NH), 8.88 ( s, 1H, 2-H ), 8.33 ( s, 1H, 5-H ), 8.13(s, 1H, 2'-H ), 7.80–7.26 ( m, 3H, 4',5',6'-H ), 7.35 ( s, 1H, 8H ), 4.02 ( s, 3H, -OCH<sub>3</sub> ), 4.00 ( s, 3H, -OCH<sub>3</sub> ). UV(MeOH): 203.0, 210.0, 228.0, 251.0, 331.0 nm. (KBr) ν<sub>max</sub>: 3191, 3022, 2940, 2836, 2576, 1629, 1516, 1444, 1276, 1153, 1060 cm<sup>-1</sup>. GC/MS m/z 406( M<sup>+</sup>, 1.52 ), 405( M<sup>+</sup>-1, 6.22 ), 281 (35.33), 207 (100.00). Found: C, 43.55; H, 3.43; N, 9.32. C<sub>16</sub>H<sub>14</sub>IN<sub>3</sub>O<sub>2</sub>.HCl requires: C, 43.34; H, 3.38; N, 9.48%.

**4-(4'-Hydroxy-3,5-diiodophenyl)-amino-6,7-dimethoxy-quinazoline (HI-P294):**

- 20 Yield 77.47%; m.p. 259.0–260.0 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.13(s, 1H, NH), 9.73(s, 1H, -OH), 8.87(s, 1H, 2-H), 8.16(s, 1H, 5-H), 8.09(s, 2H, 2', 6'-H), 7.28(s, 1H, 8H), 3.98(s, 6H, -OCH<sub>3</sub>). UV(MeOH)λ<sub>max</sub> (ε): 217.0, 227.0, 252.0 nm. IR(KBr)ν<sub>max</sub>: 3457, 3201, 2934, 2832, 2566, 1629, 1562, 1521, 1439, 1275, 1075 cm<sup>-1</sup>. GC/MS m/z: GC/MS m/z 422(M<sup>+</sup>-I, 33.53), 405(7.50), 281(86.67), 221 (51.80), 207(91.30). Found: C, 32.60; H, 2.50; N, 6.92. C<sub>16</sub>H<sub>13</sub>I<sub>2</sub>N<sub>3</sub>O<sub>3</sub>.HCl requires: C, 32.82; H, 2.39; N, 7.18%.

**4-(4'-Hydroxy-3'-iodophenyl)-amino-6,7-dimethoxyquinazoline(HI-P299)**

- 30 Yield 71.59 %; m.p. 248.0–250.0 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.32(d, 1H, NH), 10.62(s, 1H, -OH), 8.79(s, 1H, 2-H), 8.26(s, 1H, 5-H), 7.98 – 6.98(m, 3H, 2', 3', 6'-H), 7.32(s, 1H, 8H), 3.98(s, 3H, -OCH<sub>3</sub>), 3.97(s, 3H, -OCH<sub>3</sub>). UV(MeOH)λ<sub>max</sub> (ε): 217.0, 227.0, 252.0 nm. IR(KBr)ν<sub>max</sub>: 3411, 2975, 2730, 2366, 1634, 1573, 1501, 1429, 1229, 1075 cm<sup>-1</sup>. GC/MS m/z: 406(M<sup>+</sup>-1, 3.33), 405(M<sup>+</sup>-2, 7.50), 281 (M<sup>+</sup>-

1-I, 26.67 ), 253(11.80), 207(100.00). Found: C, 41.96; H, 3.40; N, 8.98.

$C_{16}H_{14}IN_3O_3 \cdot HCl$  requires: C, 41.83; H, 3.26; N, 9.15%.

**4-(4'-Iodophenyl)-amino-6,7-dimethoxyquinazoline (HI-P300):** Yield 85.24%;

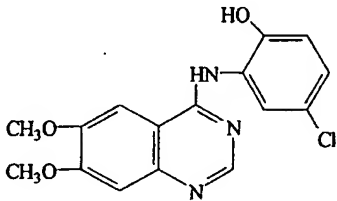
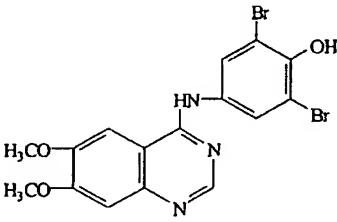
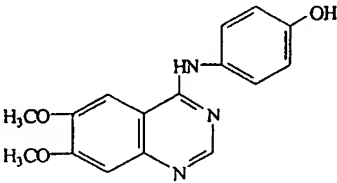
- 5 m.p. 240.0–242.0 °C.  $^1H$  NMR( DMSO- $d_6$ ) :  $\delta$  11.51 ( s, 1H, NH), 8.82 ( s, 1H, 2-H ),  
8.37 ( s, 1H, 5-H), 7.81 ( d, 2H, J= 8.4 Hz, 2', 6'- H ), 7.55 ( d, 2H, J= 8.4 Hz, 3', 5'- H  
, 7.35 ( s, 1H, 8H ), 4.01 ( s, 3H, -OCH<sub>3</sub>), 3.98( s, 3H, -OCH<sub>3</sub>). UV ( MeOH):. 217.0 ,  
227.0, 252.0 nm. IR ( KBr )  $\nu_{max}$ : 3211, 3032, 2832, 2720, 1629, 1573, 1501, 1434,  
1235,1153, 1070  $cm^{-1}$ . GC/MS m/z 406( $M^+ - 1$ , 3.33), 405( $M^+ - 2$ , 7.50), 281 ( $M^+ - 1 - I$ ,  
10 26.67 ), 253(11.80), 207(100.00). Found: C, 43.40; H, 3.39; N, 9.36.  $C_{16}H_{14}IN_3O_2 \cdot HCl$ .  
requires: C, 43.34; H, 3.38; N, 9.48%.

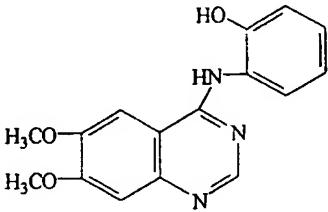
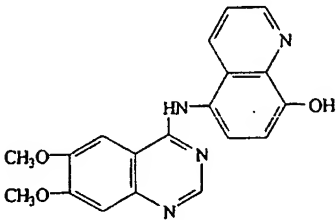
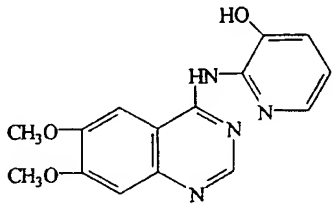
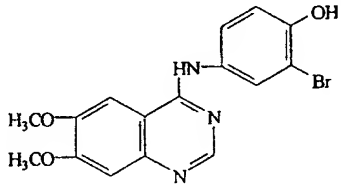
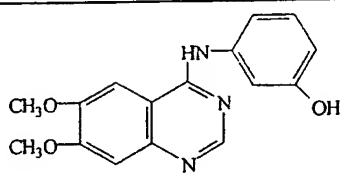
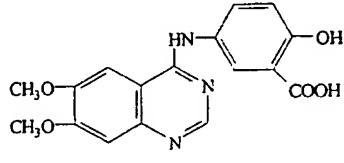
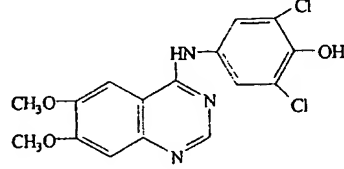
### Example 5

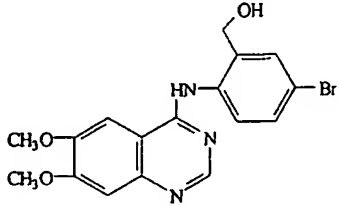
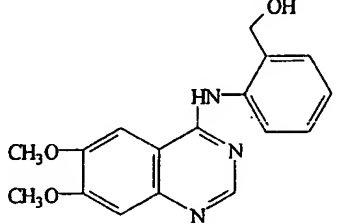
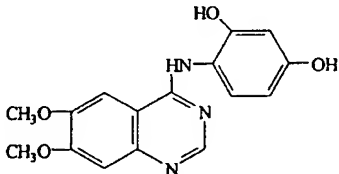
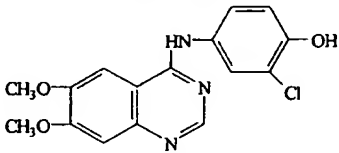
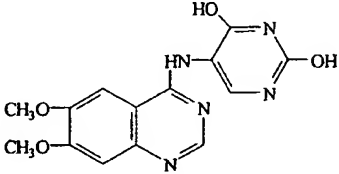
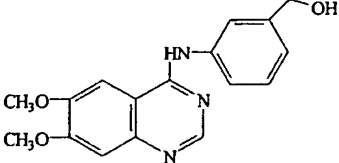
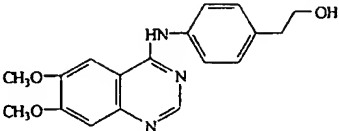
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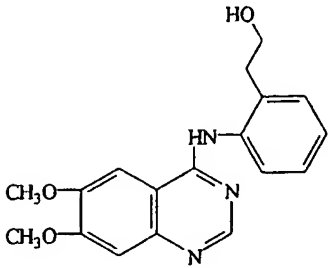
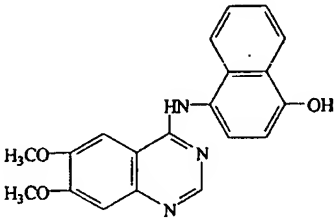
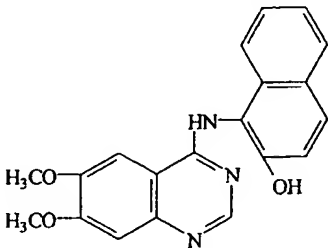
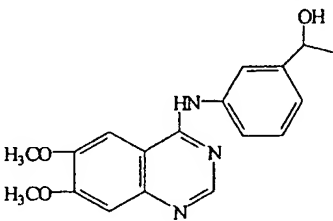
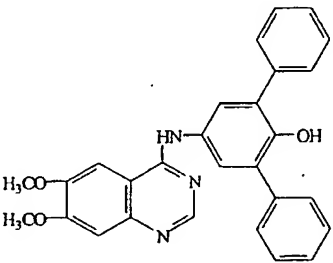
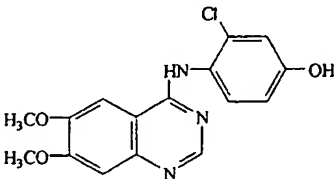
#### OH Group Substituted Quinazoline Compounds

OH group substituted quinazoline derivatives were synthesized and characterized as discussed above for Example 1. The structures and physical data are shown below:

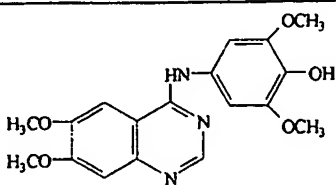
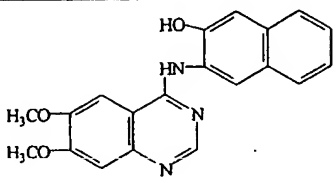
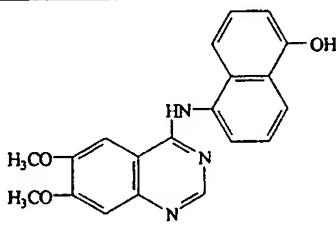
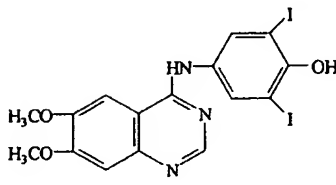
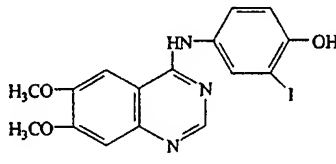
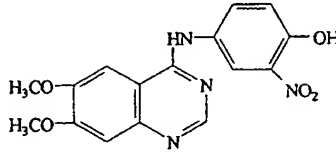
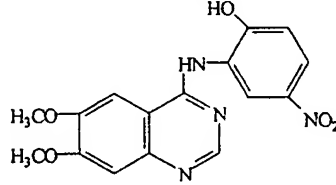
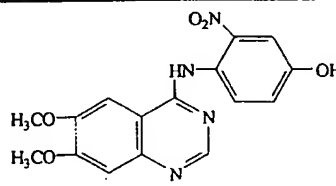
No	Name	Structure	Formula	MW
1	P-93		$C_{16}H_{14}ClN_3O_3$	331
2	P-97		$C_{16}H_{13}Br_2N_3O_3$	455
3	P-131		$C_{16}H_{15}N_3O_3$	297

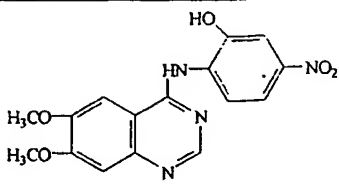
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4	P-132		$C_{16}H_{15}N_3O_3$	297
5	P-133		$C_{19}H_{16}N_4O_3$	348
6	P-150		$C_{15}H_{14}N_4O_3$	298
7	P-154		$C_{16}H_{14}BrN_3O_3$	376
8	P-180		$C_{16}H_{15}N_3O_3$	297
9	P-182		$C_{17}H_{15}N_3O_5$	341
10	P-189		$C_{16}H_{13}Cl_2N_3O_3$	365

No	Name	Structure	Formula	MW
11	P-190		$C_{17}H_{16}BrN_3O_3$	389
12	P-191		$C_{17}H_{17}N_3O_3$	311
13	P-192		$C_{16}H_{15}N_3O_4$	313
14	P-197		$C_{16}H_{14}ClN_3O_3$	331
15	P-215		$C_{14}H_{13}N_5O_4$	315
16	P-259		$C_{17}H_{17}N_3O_3$	311
17	P-265		$C_{18}H_{19}N_3O_3$	325

No	Name	Structure	Formula	MW
18	P-266		$C_{18}H_{19}N_3O_3$	325
19	P-274		$C_{20}H_{17}N_3O_3$	347
20	P-275		$C_{20}H_{17}N_3O_3$	347
21	P-276		$C_{18}H_{19}N_3O_3$	325
22	P-277		$C_{28}H_{23}N_3O_3$	449
23	P-278		$C_{16}H_{14}ClN_3O_3$	331



No	Name	Structure	Formula	MW
24	P-289		$C_{18}H_{19}N_3O_5$	357
25	P-292		$C_{20}H_{17}N_3O_3$	341
26	P-293		$C_{20}H_{17}N_3O_3$	341
27	P-294		$C_{16}H_{13}I_2N_3O_3$	549
28	P-229		$C_{16}H_{14}IN_3O_3$	423
29	P-312		$C_{16}H_{14}N_4O_5$	342
30	P-313		$C_{16}H_{14}N_4O_5$	342
31	P-315		$C_{16}H_{14}N_4O_5$	342

No	Name	Structure	Formula	MW
32	P-323		C <sub>16</sub> H <sub>14</sub> N <sub>4</sub> O <sub>5</sub>	342

**4-(3'-Chloro-6'-hydroxylphenyl)amino-6,7-dimethoxyquinazoline(HI-P93)**

yield 93.08%; m.p.295.0°C.(dec). <sup>1</sup>H NMR-DMSO-d<sub>6</sub>: δ 10.14(s, 1H, -NH), 9.16(s, 1H, -OH), 8.37(s, 1H, 2-h), 7.78(s, 1H, 5H), 7.57(d, 1H, J<sub>2,2'</sub>= 2.4Hz, 2' - H), ), 7.16(s, 1H, 8-H), 7.07(dd, 1H, J<sub>2,4</sub>=2.4 Hz, J<sub>4,5</sub>=8.7 Hz, 4' -H), 6.92(d, 1H, J<sub>4,5'</sub> - 8.7 Hz, 5'-H), 3.93(s,3H, -OCH<sub>3</sub>). 3.92(s,3H, -OCH<sub>3</sub>. UV(MeOH): 205, 229.0, 251.0, 320.0 nm. IR(KBr)ν<sub>max</sub>: 3500(br), 3430, 2835, 1622, 1512, 1432, 1259 cm<sup>-1</sup>. GC/MS m/z 333(M<sup>-</sup>=2, 13.41), 332(M<sup>-</sup>=1, 9.73), 331(M<sup>+</sup>,39.47), 314(M<sup>+</sup> -OH,100.00). 298(7.64). Found: C, 52.25; H, 4.07; N, 11.39,  
 10 C<sub>16</sub>H<sub>14</sub>ClN<sub>3</sub>O<sub>3</sub>,HCl requires: C, 52.32; H, 4.09; N, 11.44%.

**4-(3',5'-Dibromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline-(HI-P97).**

Yield 72.80%; m.p.> 300.0°C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 9.71(s, 1H, -NH), 9.39(s, 1H, -OH), 8.48(s, 1H, 2-h), 8.07(s, 2H, 2', 6'-H), 7.76(s, 1H, 5-H), 7.17(s, 15 1H, 8-H), 3.94(s, 3H, -OCH<sub>3</sub>, 3.91(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 208.0, 210.0, 245.0, 320.0 nm; IR(KBr)ν<sub>max</sub>: 3504(br), 3419, 2868, 1627, 1512, 1425, 1250, 1155 cm<sup>-1</sup>; GC/MS m/z 456(M<sup>+</sup>=1, 54.40), 455(M<sup>-</sup>, 100.00), 454(M<sup>-</sup>-1, 78.01), 439(M<sup>-</sup>-OH, 7.96), 376(M<sup>-</sup>+1-Br, 9.76), 375(M<sup>-</sup>-Br, 10.91), 360(5.23). Anal. (C<sub>16</sub>H<sub>13</sub>Br<sub>2</sub>N<sub>3</sub>O<sub>3</sub>) C, H, N.

20

**4-(4'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline(HI-P131):**

yield 84.29%; m.p. 245.0- 248.0 °C. IR(KBr)ν<sub>max</sub>: 3428, 2836, 1635, 1516, 1443, 1234 cm: <sup>1</sup>H NMR(DMSO-d<sub>6</sub>: δ 11.21(s, 1H, -NH), 9.70(s, 1H, -OH), 8.74(s, 1H, 2-h), 8.22(s, 1H, 5-h), 7.40(d, 2H, J = 8.9.Hz, 2',6'-H), 7.29(s, 1H, 8-H), 6.85(d, 2H, J = 8.9 Hz, 3', 5'-H), 3.98(s, 3H, -OCH<sub>3</sub>, 3.97(s, 3H, -OCH<sub>2</sub>). GC/MS m/z 298  
 25 (M<sup>-</sup>=1, 100.00), 297(M<sup>-</sup>, 26.6), 296(M<sup>+</sup>-1, 12.5). Anal. (C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>HCl) Cl, H, N.

**4-(2'-Hydroxylphenyl)-amino-6,7-dimethoxyquinazoline(HI-P132):**

yield 82.49%; m.p. 255.0-258.0 °C. IR(KBr)ν<sub>max</sub>: 3500 (br), 3425, 2833, 1625, 1512,

1456, 1251, 1068  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR(DMSO- $d_6$ ):  $\delta$  9.78(s, 1H, -NH), 9.29(s, 1H, -OH), 8.33(s, 1H, 2-h), 7.85(s, 1H, 5-H), 7.41–6.83(m, 4H, 3',4', 5', 6'-H), 7.16(s, 1H, 8-H), 3.93(s, 3H, -OCH<sub>3</sub>), 3.92(s, 3H, -OCH<sub>3</sub>), 280( $M^+$ -OH, 10.0). Anal. ( $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_3$ , HCl) C, H, N.

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*4-[(8'-Hydroxyquinoline)-5'-Jamino-6,7-dimethoxyquinazoline(HI-P133)]* yield 83.51%; m.p. 238.0–239.0°C.  $^1\text{H}$  NMR(DMSO- $d_6$ ):  $\delta$  10.12(br,s, 1H, -NH), 8.93–7.09 M, 8H, 2, 5, 2', 3', 4', 6', 7'-H), 4.04(s,3H, -OCH<sub>3</sub>), 3.96(s,3H, -OCH<sub>3</sub>). UV(MeOH): 204.0, 245.0, 332.0 nm. IR(KBr) $\nu_{\text{max}}$ : 3425(br), 2935, 1632, 1510, 1437, 1273  $\text{cm}^{-1}$ . GC/MS  $m/z$  349( $M^-$  = 1,100.00), 348( $m^+$ , 26.56), 307(38.50), 289 (21.00).

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*4-[(3'-Hydroxypyridine)-2']-amino-6,7-dimethoxyquinazoline(HI-P150)* Yield 78.65%; m.p. 185.0–187.0 °C.  $^1\text{H}$  NMR(DMSO- $d_6$ ):  $\delta$  10.08(br,s, 1H, -NH), 8.52(s, 1H, 2-H), 7.88–7.86(m, 1H, 6'-H), 7.60(s, 1H, 5-H), 7.39–7.35(m, 1H, 4'-H), 7.32(s, 1H, 8-H), 6.63–6.58(m, 1H, 5'-H), 5.96(s, 1H, -OH), 3.97(s,3H, -OCH<sub>3</sub>), 3.94(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 204.0, 238.0, 321.0 nm. IR(KBr) $\nu_{\text{max}}$ : 3500, 3446, 2960, 1475, 1236, 1375, 1182  $\text{cm}^{-1}$ . GC/MS  $m/z$  299( $M^-$  = 1, 100), 298( $M^+$ , 34), 289(11), 291(9). Found: C, 60.26; H, 4.81; N, 18.68.  $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_5$ , requires: C, 60.26; H, 4.81; N, 18.68%.

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*4-(3'-Bromo-4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline(HI-P154);* yield 89.90%; m.p.233.0–233.5 °C.  $^1\text{H}$  NMR(DMSO- $d_6$ ): 10.08(s, 1h, -NH), 9.38(s, 1H, -OH), 8.40(s, 1H 2-H), 7.89(d, 1H,  $J_{2,6'} = 2.7$  Hz, 2'-H), 7.75(s, 1H, 5-h), 7.55(dd, 1H,  $J_{5,6'} = 9.0$  Hz,  $J_{2,6'} = 2.7$  Hz, 6'-H), 7.14(s, 1H, 8-H), 6.97(d, 1H,  $J_{5,6'} = 9.0$  Hz, 5'-H), 3.92(s, 3H, -OCH<sub>3</sub>), 3.90(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 203.0, 222.0, 25.0, 335.0 nm. IR(KBr) $\nu_{\text{max}}$ : 3431(br), 2841, 1624, 1498, 1423, 1244  $\text{cm}^{-1}$ . GC/MS  $m/z$  378( $M^+$  = 2, 90.68), 377( $M^+$  = 1, 37.49), 376( $M^+$ , 100.00), 360( $MK^+$ , 3.63), 298(28.86), 282 (6.65). Anal. ( $\text{C}_{16}\text{H}_{14}\text{BrN}_3\text{O}_3$ ,HCl) C, H, N.

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*4-(3'-Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline(HI-P180)* Yield 71.55%; m.p. 256.0–258.0 °C. IR(KBr) $\nu_{\text{max}}$ : 3394, 2836, 1626, 1508, 1429, 1251  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR(DMSO- $d_6$ ): 9.41(s, 1H, -NH), 9.36(s, 1H, -OH), 8.46(s, 1H, 2-

H), 7.84(s, 1H, 5-H), 7.84-6.50(m, 4H, 2', 4', 5', 6' -H), 7.20(s, 1H, 8-H), 3.96(s, 3H, -OCH<sub>3</sub>), 3.93(s, 3H -OCH<sub>3</sub>). GC/MS m/z: (C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>.HCl) C, H, N.

5 **4-(4'-Hydroxyl-3'-Carboxyphenyl)-amino-6,7-dimethoxyquinazoline (HI-P182)** Yield 79.25%; m.p. > 300.0 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 10.53(s, 1H, -NH), 8.53(s, 1H, 2-H), 8.10-78.2(m, 3H, 2', 5', 6' -H), 7.26(s, 1H, 5-H), 6.9(s, 1H, 8H), 4.01(s, 3H, -OCH<sub>3</sub>), 3.99(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 210.0, 239.0, 335.0 nm. IR(KBr)<sub>max</sub> 3421, 2839, 1686, 1631, 1508, 1491, 1280 cm<sup>-1</sup>. GC/MS m/z 341(M<sup>+</sup>, 7.91), 323(M<sup>+</sup> - OH, 12.19), 297(M<sup>+</sup> - COOH, 12.35), 296(M<sup>+</sup> - COOH - 1.1760), 295(M<sup>+</sup> - COOH - 2, 28.65), 206 (11.28).

15 **4-(4'-Hydroxyl-3',5'-dichlorophenyl)-6,7-dimethoxyquinazoline(HI-P189)** Yield 79.45%; m.p. 293.0-295.0 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): 11.32(s, 1H, -NH), 10.34(a, 1H, -OH), 8.87(s, 1H, 2-H), 8.29(s, 1H, 5-H), 7.90(s, 2H, 2', 6'-H), 7.32(s, 1H, 8-H), 4.01(s, 3H, -OCH<sub>3</sub>), 3.99(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 213.0, 232.0, 250.0, 335.0 nm. IR(KBr)<sub>max</sub>: 3479, 2564, 1641, 1579, 1429, 1282, 1147 cm<sup>-1</sup>. GC/MS m/z 367(M<sup>+</sup> + 2, 66.57), 366(M<sup>+</sup> + 1, 75.91), 365(M<sup>+</sup>, 100.00), 364(M<sup>+</sup>-1, 94.08), 349(M<sup>+</sup>-OH, 11.16). Anal. (C<sub>16</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub>) C, H, N. Found: C, 48.93; H, 4.51; N, 10.00. -H<sub>1</sub>-Cl<sub>2</sub>N<sub>3</sub>O<sub>3</sub>. HCl requires: C, 48.80; H, 4.31; N, 10.04%.

25 **4-(4'-Bromo-6'-hydroxymethylphenyl)-amino-6,7-dimethoxyquinazoline(HI-P190)** Yield 70.08%; m.p. 222.0-223.0 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.30(s, 1H, -OH), 8.22(s, 1H, -NH)O, 7.77.7.23(m, 5H, 5, 8, 2', 3', 5'-H), 4.49(s, 2H, PhCH<sub>2</sub>-H), 4.01(s, 3H, -OCH<sub>3</sub>), 3.90(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 207.0, 250.0, 332.0 nm. IR(KBr)<sub>max</sub>: 3446, 2829, 2752, 1652, 1560, 1471, 1365, 1280 cm<sup>-1</sup>. GC/MS m/z 391(M<sup>+</sup>=1, 29.33), 389(M<sup>+</sup>, 29.82), 360(M<sup>+</sup>-CH<sub>2</sub>OH, 50.76), 358(52.39), 311(18.33), 280(43.20), 206(62.80), 191(100.00). Anal. (C<sup>17</sup>H<sup>16</sup>BrN<sub>3</sub>O<sub>3</sub>.HCl) C, H, N.

30 **4-(6'-Hydroxymethylphenyl)-amino-6,7-dimethoxyquinazoline(HI-P191)** Yield 78.45%; m.p. 215.0-218.0 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.54(s, 1H, -NH)O, 8.70(s, 1H, 2-H), 8.34(s, 1H, 5-H), 7.62-7.33(m, 4H, 3', 4', 5', 6'-H), 7.39(s, 1H, 8-H), 4.49(s, 2H, PhCH<sub>2</sub>OH), 3.99(s, 3H, -OCH<sub>3</sub>), 3.98(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 209.0, 224.0, 246.0, 335.0 nm. IR(KBr)<sub>max</sub>: 3421, 2941, 1675,

2606,  $\nu$  128, 1508, 1437, 1244  $\text{cm}^{-1}$ . GC/MS  $m/z$  311( $M^+$ , 38.07), 310( $M^+ - 1$ , 27.04), 280( $M^+ - \text{CH}_2\text{OH}$ , 100.00), 206(17.24), 191(51.34).

**4-(2',4'-Dihydroxyphenyl)-amino-6,7-dimethoxyquinazoline (HI-P192)** Yield 86.25%; m.p. 240.0 °C(dec).  $^1\text{H}$  NMR(DMSO- $d_6$ ): 10.92(s, 1H, -NH), 9.76(s, 1H, -OH), 9.59(s, 1H, -OH), 8.67(s, 1H, 20H), 8.1.9(s, 1H, 8-H), 7.36(s, 1H, 50H), 705(d, 1H,  $J = 8.7$  Hz, 1'-H), 6.51(s, 1H, 5'-H), 6.31(d, 1H,  $J = 8.7$  Hz, 3'-H), 3.98(s, 6H, -OCH<sub>3</sub>). UV(MeOH): 206.0, 209.0, 223.0, 250.0, 342.0, 486 nm. IR(KBr) $\nu_{\text{max}}$ : 3391, 3139, 2938, 2850, 1633, 1607, 1567, 1509, 1447, 1359, 1220, 1189, 1055  $\text{cm}^{-1}$ . GC/MS  $m/z$ : 314( $M^+ = 1$ , 13.00), 313( $m^+$ , 72.80), 312( $m^+ - 1$ , 10.20), 296(5.24), 206(17.50).

**4-(2',3'-Dihydroxyphenyl)-amino-6,7-dimethoxyquinazoline (HI-P192)** Yield 86.25%; m.p. 240.0 °C(dec).  $^1\text{H}$  NMR(DMSO- $d_6$ ): 10.00(s, 1H, -NH), 9.37(s, 1H, -OH), 8.41(s, 1H, 2-H), 7.78(s, 1H, 5-H), 7.49(d, 1H,  $J_{2,3'} = 2.7$  Hz, 2'-H), 7.55(dd, 1H,  $J_{5',6'} = 9.0$  Hz,  $J_{2',6'} = 2.7$  Hz, 6'-H), 7.16(s, 1H, 8-H), 6.97(d, 1H,  $J_{5',6'} = 9.0$  Hz, 5'-H), 3.93(s, 3H, -OCH<sub>3</sub>), 3.91(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 209.0, 224.0, 249.0, 330.0 nm. IR(KBr) $\nu_{\text{max}}$ : 3448, 2842, 1623, 1506, 1423, 1241  $\text{cm}^{-1}$ . GC/MS  $m/z$ : 341( $M^+$ , 100.00), 326( $M^+ - \text{CH}_3$ , 98.50), 310( $M^+ - \text{OCH}_3$ , 12.5), 295(9.0), 189(13.5), 155(13.8). Found: C, 52.35; H, 4.16; Cl, 19.15; N, 11.39. C<sub>16</sub>H<sub>14</sub>ClN<sub>3</sub>O<sub>3</sub>HCl requires: C, 52.32; H, 4.09; Cl, 19.07; N, 11.44%.

**4-(2',4'-Dihydroxyl-1',3'-diazine-5')-amino-6,7-dimethoxyquinazoline (HI-P215)** (Yield 89.23%, m.p. > 300.0 °C)  $^1\text{H}$  NMR(DMSO- $d_6$ ):  $\delta$  8.59(s, 1H, 2-H), 7.89(s, 1H, 5-H), 7.60(d, 1H, 6'-H), 7.09(s, 1H, 8-H), 3.78(s, 3H, -OCH<sub>3</sub>), 3.76(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 222.0, 246.0, 331.0 nm. IR(KBr) $\nu_{\text{max}}$ : 3446, 3212, 3057, 1750, 1682, 1620, 1590, 1511, 1420, 1265  $\text{cm}^{-1}$ . GC/MS  $m/z$ : 315( $M^+ .57.52$ ), 206(46.50), 191(18.21), 127(100.00).

**4-(3'-Hydroxymethylphenyl)-amino-6,7-dimethoxyquinazoline (HI-P259)** Yield 74.28%; m.p. 230.0-232.0 °C.  $^1\text{H}$  NMR(DMSO- $d_6$ ):  $\delta$  11.29(s, 1H, -NH), 8.83(s, 1H, 2-H), 8.28(s, 1H, 5-H), 7.61-7.25(m, 4H, 2',4',5',6'-H), 7.36(s, 1H, 8H), 4.57(s, 2H, -CH<sub>2</sub>OH), 4.02(s, 3H, -OCH<sub>3</sub>), 4.00(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 207.0, 224.0, 251.0, 334.0 nm. IR(KBr) $\nu_{\text{max}}$ : 3500, 3029, 1639, 1589, 1514, 1456, 1284  $\text{cm}^{-1}$ . GC/MS  $m/z$ : 281( $M^+ + 1 - \text{CH}_2\text{OH}$ , 54.00), 280( $M^+ - \text{CH}_2\text{OH}$ , 100.00).

Found: C, 58.68; H, 5.30; N, 12.02.  $C_{16}H_{15}N_3O_2 \cdot HCl$  requires: C, 58.79; H, 5.19; N, 12.10%.

- 4-[4'-(2''-Hydroxyethylphenyl)]-amino-6,7-dimethoxyquinazoline (HI-P265) Yield 92.30%; m.p. 235.0–240.0 °C.  $^1H$  NMR(DMSO- $d_6$ ):  $\delta$  11.44(s, 1H, -NH), 8.79(s, 1H, 2-H), 8.34(s, 1H, 5-H), 7.56(d, 2H, J=8.1 Hz, 2',6'-H), 7.34(d, 2H, J=8.1 Hz, 3',5'-H), 7.31(s, 1H, 8H), 4.00(s, 3H, -OCH<sub>3</sub>), 3.99(s, 3H, -OCH<sub>3</sub>), 3.64(t, 2H, J=6.9 Hz, 1''-H), 2.77(t, 2H, J=6.9 Hz, 2''-H). UV(MeOH): 204.0, 226.0, 251.0, 335.0 nm. IR(KBr) $\nu_{max}$ : 3361, 3015, 2706, 1628, 1581, 1514, 1432, 1282  $cm^{-1}$ . GC/MS m/z: 281(17.00), 253(10.00), 207(100.00).
- 10 4-[2'-(2''-Hydroxyethylphenyl)]-amino-6,7-dimethoxyquinazoline (HI-P266) Yield 87.69%; m.p. 228.0–230.0 °C.  $^1H$  NMR-DMSO- $d_6$ ):  $\delta$  11.32(s, 1H, -NH), 8.74(s, 1H, 2'-H), 8.13(s, 1H, 5-H), 7.46–7.34(m, 4H, 3',4',5,6'-H), 7.32(s, 1H, 8H), 4.00(s, 3H, -OCH<sub>3</sub>), 3.99(s, 3H, -OCH<sub>3</sub>), 3.58(t, 2H, J=7.2 Hz, 1''-H), 2.75(t, 2H, J=7.2 Hz, 2''-H). UV(MeOH): 210.0, 226.0, 249.0, 332.0 nm. IR(KBr) $\nu_{max}$ : 3366, 3226, 3056, 2917, 2685, 2163, 1571, 1514, 1467, 1277  $cm^{-1}$ . GC/MS m/z: 281(20.00), 253(9.00), 207(100.00).
- 20 4-(1'-Naphthol-4')-amino-6,7-dimethoxyquinazoline (HI-P274) Yield 79.26; m.p. 205.0–208.0 °C.  $^1H$  NMR-DMSO- $d_6$ ):  $\delta$  11.64(s, 1H, -NH), 10.61(s, 1H, -OH), 8.59(s, 1H, 2-H), 8.41(s, 1H, 5-H), 8.22–6.98(m, 5H, 3', 5', 6', 7',8'-H), 7.40(s, 1H, 8H), 4.00(s, 3H, -OCH<sub>3</sub>), 3.99(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 208.0, 215.0, 225.0, 240.0, 330.0 nm. IR(KBr) $\nu_{max}$ : 3438, 3211, 3061, 2932, 2834, 1633, 1576, 1509, 1437, 1380, 1276, 1215  $cm^{-1}$ . GC/MS m/z: 281(51.00), 253(22.00), 207(88.00). Found: C, 62.26; H, 4.87; N, 10.77.  $C_{20}H_{17}N_3O_3 \cdot HCl$  requires: C, 62.66; H, 4.70; N, 10.96%.
- 25 4-(2'-Naphthol-1')-amino-6,7-dimethoxyquinazoline (HI-P275) Yield 83.17%; m.p. 218.0–220.0 °C.  $^1H$  NMR(DMSO- $d_6$ ):  $\delta$  11.33(s, 1H, -NH), 10.22(s, 1H, -OH), 8.62(s, 1H, 2-H), 8.40(s, 1H, 5-H), 7.98–7.31(m, 6H, 3',4',5',6',7',8'-H), 7.41(s, 1H, 8H), 4.02(s, 3H, -OCH<sub>3</sub>), 4.00(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 206.0, 210, 219.0, 225.0, 230.0, 340.0 nm. IR(KBr) $\nu_{max}$ : 3391, 3165, 3051, 2938, 2840, 1628, 1576, 1504, 1437, 1281, 1215  $cm^{-1}$ . GC/MS m/z: 348( $M^+$ , 7.00), 347( $M^+$ , 100.00), 346( $M^+$ , 1.22.00), 331(15.00), 330(12.00), 281(23.00),
- 30

253(12.00), 207(49.00). Found: C, 62.91; H, 4.76; N, 10.75.  $C_{20}H_{11}N_3O_3 \cdot HCl$  requires: C, 62.66; H, 4.70; N, 10.96%.

**4-[3'-(1''-Hydroxyethyl)]-amino-6,7-dimethoxyquinazoline (HI-P276)** Yield 79.21%; m.p. 215.0–218.0 °C.  $^1H$  NMR(DMSO- $d_6$ ):  $\delta$  11.40(s, 1H, -NH), 8.81(s, 1H, 20H), 8.31(s, 1H, 5-H)O, 7.60–7.26(m, 4H, 2',4',5',6'-H), 7.41(s, 1H, 8H), 4.65(q, 1H, J= 6.6Hz, -CH(OH)CH<sub>3</sub>), 4.00(s, 3H, -OCH<sub>3</sub>), 3.98(s, 3H, -OCH<sub>3</sub>), 1.350(d, 3H, J= 6.6 Hz, -CH<sub>3</sub>). UV(MeOH): 204.0, 216.0, 220.0, 224.0, 250.00, 348.0 nm. IR(KBr) $\nu_{max}$ : 3407, 3030, 2977, 2840, 1643, 1591, 1514, 1463, 1370, 1282, 1230  $cm^{-1}$ . GC/MS m/z: 325( $M^+ + 1$ , 67.00), 324( $M^+$ , 100.00), 323( $M^+$  10 1.22.00), 308(17.00), 307(56.00), 306(21.00), 281(2.00), 280(8.00), 264(6.00).

**4-(4'-Hydroxy-3',5'-diphenylphenyl)-amino-6,7-dimethoxyquinazoline (HI-P277)** Yield 76.11%; m.p. 255.0–257.0 °C.  $^1H$  NMR(DMSO- $d_6$ ):  $\delta$  11.50(s, 1H, -NH), 8.80(d, d, 2H, 2',6'-H), 8.58(s, 1H, 5-H), 7.60–7.30(m, 10H, 3', 5', Ph-H), 7.39(s, 1H, 8H), 4.00(s, 3H, -OCH<sub>3</sub>), 3.97(s, 3H, -OCH<sub>3</sub>), 1.350(d, 3H, J= 6.6 Hz, -CH<sub>3</sub>). UV(MeOH): 210.0, 214.0, 229.0, 239.0, 345.0, 248.0, 352.0 nm. 15 IR(KBr) $\nu_{max}$ : 3520, 3218, 3023, 2935, 1630, 1562, 1518, 1457, 1281, 1234  $cm^{-1}$ . GC/MS m/z: 281(35.00), 267(6.00), 253(10.00), 207(100.00).

**4-(4'-Hydroxyl-2'-chlorophenyl)-amino-6,7-dimethoxyquinazoline (HI-P2878)** Yield 81.44%; m.p. 245.0–247.0 °C.  $^1H$  NMR(DMSO- $d_6$ ):  $\delta$  11.39(s, 1H, -NH)O, 10.30(s, 1H, -OH), 8.75(s, 1H, 2-H), 8.24(s, 1H, 5-H), 7.38–6.85(m, 3H, 3',5',6'-H), 7.37(s, 1H, 8H), 3.98(s, 3H, -OCH<sub>3</sub>), 3.96(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 222.0, 234.0, 239.0, 245.0, 254.0, 348.0 nm. IR(KBr) $\nu_{max}$ : 3448, 3242, 3144, 3025, 2917, 2834, 1638, 1591, 1514, 1437, 1365, 1277, 1209  $cm^{-1}$ . GC/MS m/z: 332( $M^+ + 1$ , 5.00), 331( $M^+$ , 17.00), 330( $M^+ - 1$ , 5.00), 297(17.00), 296(100.00), 281(18.00), 25 280(29.00), 253(9.00).

**4-(2'-Hydroxy-naphthyl-3')-amino-6,7-dimethoxyquinazoline (HI-P292)** Yield 87.41%; m.p. 277.0–279.0 °C.  $^1H$  NMR(DMSO- $d_6$ ):  $\delta$  11.38(s, 1H, -NH)O, 10.35(s, 1H, -OH), 8.73(s, 1H, 2-H), 8.25(s, 1H, 5-H), 7.93–7.30(m, 6H, 1', 4', 5', 6', 7', 8'-H), 7.37(s, 1H, 8H)O, 4.00(s, 6H, -OCH<sub>3</sub>). UV(MeOH): 204.0, 221.0, 30 224.0, 230.0, 256.0, 344.0 nm. IR(KBr) $\nu_{max}$ : 3479, 3386, 3036, 2901, 1632, 1581, 1504, 1437, 1281  $cm^{-1}$ . GC/MS m/z: 281(41.00), 253(11.00), 207(100.00). Found:

C, 62.87; H, 4.83; N, 10.78.  $C_{20}H_{17}N_3O_3 \cdot HCl$  requires: C, 62.66; H, 4.70, N, 10.96%.

**4-(1'-Hydroxy-naphthyl-5')-amino-6,70-dimethoxyquina-zoline(HI-P293)**

5 Yield 87.21%; m.p. 204.0–205.0 °C.  $^1H$  NMR(DMSO- $d_6$ ):  $\delta$  11.73(s, 1H, -NH), 10.43(s, 1H, -OH), 8.65(s, 1H, 2-H), 8.38(s, 1H, 5-H), 8.21–6.95(m, 6H, 2', 3', 4', 6', 7', 8'-H), 7.33(s, 1H, 8H)O, 4.00(s, 6H, -OCH<sub>3</sub>). UV(MeOH): 204.0, 214.0, 224.0, 229.0, 235.0 348 nm. IR(KBr) $\nu_{max}$ : 3449, 3335, 3102, 2927, 1633, 1571, 1509, 1437, 1287  $cm^{-1}$ . Found: C, 62.23; H, 4.96; N, 10.89.  $C_{20}H_{17}N_3O_3 \cdot HCl$  requires: C, 62.66; H, 4.70; N, 10.96%.

**4-(4'-Hydroxy-3,5-diiodophenyl)-amino-6,7-dimethoxy-quinazoline(HI-P294)**

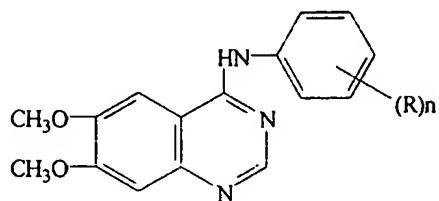
Yield 77.47%; m.p. 259.0–260.0 °C.  $^1H$  NMR(DMSO- $d_6$ ):  $\delta$  11.13(s, 1H, NH), 9.73(s, 1H, -OH), 8.87(s, 1H, 2-H), 8.16(s, 1H, 5-H), 8.09(s, 2H, 1', 6'-H), 7.28(s, 1H, 8H), 3.98(s, 6H, -OCH<sub>3</sub>). UV(MeOH) $\lambda_{max}$ : 217.0, 227.0, 252.00 nm. IR(KBr) $\nu_{max}$ : 3457, 3201, 2934, 2832, 2566, 1629, 1562, 1521, 1439, 1275, 1075  $cm^{-1}$ . GC/MS m/z: GC/MS m/z 422(M<sup>+</sup>-1.33.53), 405(7.50), 281(86.67), 221(51.80), 207(91.30). Found: C, 32.60; H, 2.50; N, 6.92.  $C_{16}H_{13}I_2N_3O_3 \cdot HCl$  requires: C, 32/82; H, 2.39; N, 7.18%.

**4-(4'-Hydroxy-3'-iodophenyl)-amino-6,7-dimethoxyquinazoline(HI-P299)**

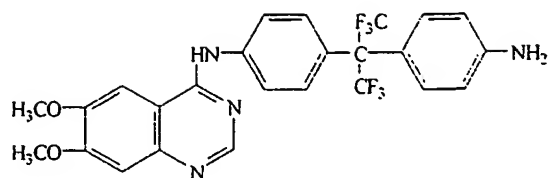
20 Yield 71.59%; m.p. 248.0–250.0 °C.  $^1H$  NMR(DMSO- $d_6$ ):  $\delta$  11.32(d, 1H, NHO), 10.62(s, 1H, -OH), 8.79(s, 1H, 2-H), 8.26(s, 1H, 5-H), 7.98 – 6.98(m, 3H, 2', 3', 6'-H), 7.32(s, 1H, 8H), 3.98(s, 3H, -OCH<sub>3</sub>), 3.97(s, 3H, -OCH<sub>3</sub>). UV(MeOH)  $\lambda_{max}$  ( $\epsilon$ ): 217.0, 227.0, 252.0 nm. IR(KBr) $\nu_{max}$ : 3411, 2975, 2730, 2366, 1634, 1573, 1501, 1429, 1229, 1075  $cm^{-1}$ . GC/MS m/z: 406(M<sup>+</sup>-1.3.33), 405(M<sup>+</sup>-2, 7.50), 281(M<sup>+</sup>-1-I, 26.67), 253(11.80), 207(100.00). Found: C, 41.96; H, 3.40; N, 8.98.  $C_{16}H_{14}IN_3O_3 \cdot HCl$  requires: C, 41.83; H, 3.26; N, 9.15%.



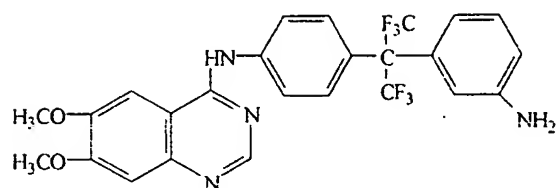
Table 5 Fluoroquinazoline Derivatives



(HI-P352)		(HI-P353)	
No	R	Formular	MW
HI-P144	2-F, 3-F, 5-F, 6-F, 4-Br	C <sub>16</sub> H <sub>10</sub> BrF <sub>4</sub> N <sub>3</sub> O <sub>2</sub>	432
HI-P214	2-F, 4-Br	C <sub>16</sub> H <sub>13</sub> BrFN <sub>3</sub> O <sub>2</sub>	378
HI-P218	3-CF <sub>3</sub>	C <sub>17</sub> H <sub>14</sub> F <sub>3</sub> N <sub>3</sub> O <sub>2</sub>	349
HI-P219	4-OCF <sub>3</sub>	C <sub>17</sub> H <sub>14</sub> F <sub>3</sub> N <sub>3</sub> O <sub>3</sub>	365
HI-P221	4-F	C <sub>16</sub> H <sub>14</sub> FN <sub>3</sub> O <sub>2</sub>	299
HI-P223	4-CF <sub>3</sub>	C <sub>17</sub> H <sub>14</sub> F <sub>3</sub> N <sub>3</sub> O <sub>2</sub>	349
HI-P224	3-F	C <sub>16</sub> H <sub>14</sub> FN <sub>3</sub> O <sub>2</sub>	299
HI-P228	2-CF <sub>3</sub>	C <sub>17</sub> H <sub>14</sub> F <sub>3</sub> N <sub>3</sub> O <sub>2</sub>	349
HI-P232	4-SO <sub>2</sub> F	C <sub>16</sub> H <sub>14</sub> FN <sub>3</sub> O <sub>4</sub> S	363
HI-P264	2-F	C <sub>16</sub> H <sub>14</sub> FN <sub>3</sub> O <sub>2</sub>	299
HI-P352	*	C <sub>25</sub> H <sub>20</sub> F <sub>6</sub> N <sub>4</sub> O <sub>2</sub>	522
HI-P353	*	C <sub>25</sub> H <sub>20</sub> F <sub>6</sub> N <sub>4</sub> O <sub>2</sub>	522
HI-P364	3-OCF <sub>3</sub>	C <sub>17</sub> H <sub>14</sub> F <sub>3</sub> N <sub>3</sub> O <sub>3</sub>	365
HI-P365	2-OCF <sub>3</sub>	C <sub>17</sub> H <sub>14</sub> F <sub>3</sub> N <sub>3</sub> O <sub>3</sub>	365
HI-P366	3-CF <sub>3</sub> , 5-CF <sub>3</sub> ,	C <sub>18</sub> H <sub>13</sub> F <sub>6</sub> N <sub>3</sub> O <sub>2</sub>	417
HI-P367	2-CF <sub>3</sub> , 5-CF <sub>3</sub> ,	C <sub>18</sub> H <sub>13</sub> F <sub>6</sub> N <sub>3</sub> O <sub>2</sub>	417
HI-P369	3-F, 4-OH	C <sub>16</sub> H <sub>14</sub> FN <sub>3</sub> O <sub>3</sub>	315
HI-P408	3-F, 5-F, 4-OH	C <sub>16</sub> H <sub>13</sub> F <sub>2</sub> N <sub>3</sub> O <sub>3</sub>	333



HI-P353



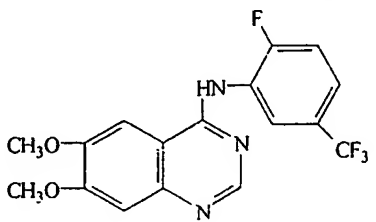
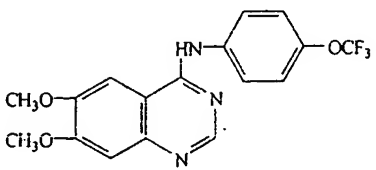
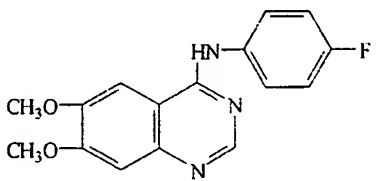
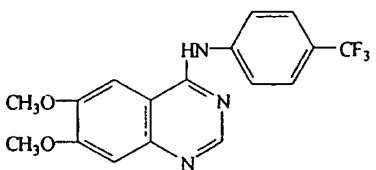
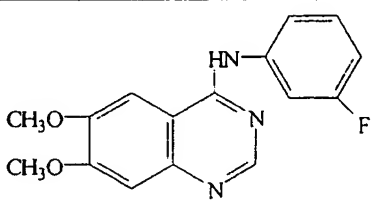
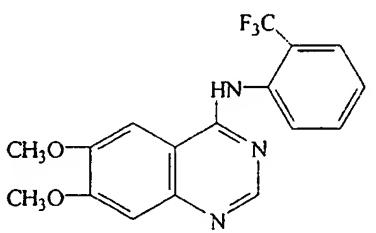
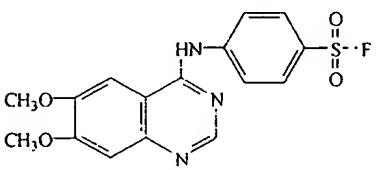
HI-P352

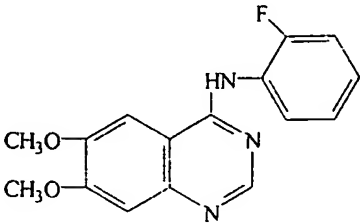
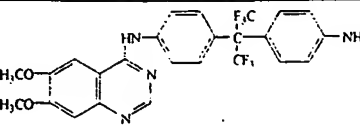
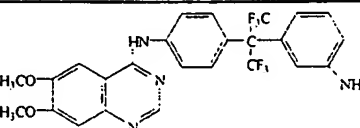
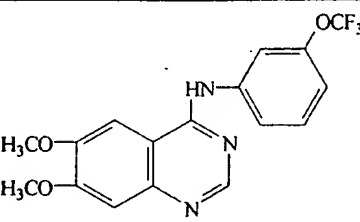
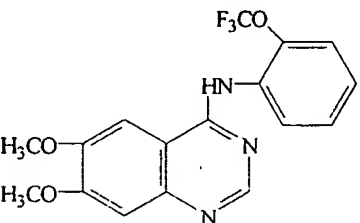
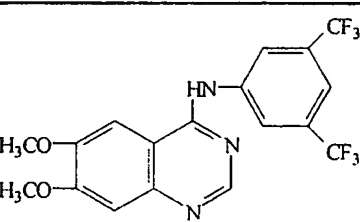
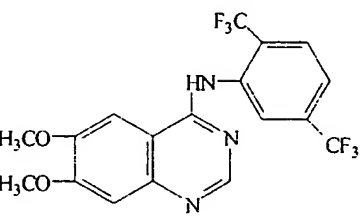
5

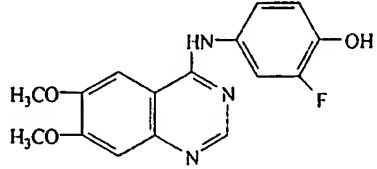
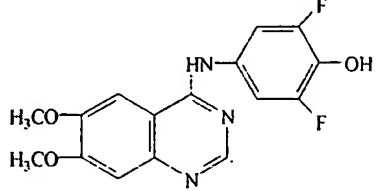
**Example 6****Fluorine Substituted Quinazoline Compounds**

10 Fluorine substituted quinazoline derivatives were synthesized and characterized as discussed above for Example 1. The structures and physical data are shown below:

No	Name	Structure	Formula	MW
1	P-144		$C_{16}H_{10}BrF_4N_3O_2$	432
2	P-214		$C_{16}H_{13}BrFN_3O_2$	378

No	Name	Structure	Formula	MW
3	P-218		$C_{17}H_{13}F_4N_3O_2$	367
4	P-219		$C_{17}H_{14}F_3N_3O_3$	365
5	P-221		$C_{16}H_{14}FN_3O_2$	299
6	P-223		$C_{17}H_{14}F_3N_3O_2$	349
7	P-224		$C_{16}H_{14}FN_3O_2$	299
8	P-228		$C_{17}H_{14}F_3N_3O_2$	349
9	P-232		$C_{16}H_{14}F_2SN_3O_4$	363

No	Name	Structure	Formula	MW
10	P-264		$C_{16}H_{14}FN_3O_2$	299
11	P-352		$C_{25}H_{20}F_6N_4O_2$	522
12	P-353		$C_{25}H_{20}F_6N_4O_2$	522
13	P-364		$C_{17}H_{14}F_3N_3O_3$	365
14	P-365		$C_{17}H_{14}F_3N_3O_3$	365
15	P-366		$C_{18}H_{13}F_6N_3O_2$	417
16	P-367		$C_{18}H_{13}F_6N_3O_2$	417

No	Name	Structure	Formula	MW
17	P-369		$C_{16}H_{14}FN_3O_3$	315
18	P-408		$C_{16}H_{13}F_2N_3O_3$	333

**4-(2',3',5',6'-Tetrafluoro-4'-bromophenyl)-amino-6,7-dimethoxyquinazoline (HI-P144)** The yield 78.24%; m.p. 180.0–182.0 °C.  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  7.78(s, 1H, 2-H), 7.53(s, 1H, 5-H), 6.79(s, 1H, 8-H), 3.81(s, 3H, -OCH<sub>3</sub>), 3.3.79(s, 3 H, -OCH<sub>3</sub>). Found: C, 41.12; H, 2.41; N, 9.89.  $C_{10}H_{10}BrF-N_3O_2 \cdot HCl$  requires: C, 41.11; H, 2.36; N, 9.93%.

**4-(2'-Fluoro-4'-bromophenyl)-amino-6,7-dimethoxyquinazoline (HI-P214)**  
The yield 77.21%; m.p. 247.0–252.0 °C.  $^1H$  NMR(DMSO- $d_6$ ):  $\delta$  8.57(s, 1H, 2-H), 7.91(s, 1H, 5-H), 7.57 (d, 1H, 3'-H), 7.34(m, 2H, 5',6'-H), 7.07(s, 1H, 8-H), 3.78(s, 3H, -OCH<sub>3</sub>), 3.77(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 204.0, 215.0, 250.0, 330.0 nm.. IR(KBr)  $\nu_{max}$ : 3431, 2629, 1633, 1580, 1511, 1420, 1278  $cm^{-1}$ . GC/MS m/z 379( $M^+ + 1$ , 34.39), 378( $M^-$ , 31.33), 377( $M^- - 1$ , 39.08), 360(62.05), 359 (31.58), 358(62.57), 357(19.81), 299(19.31), 298(100.00), 282(17.88), 240(28.76).

15

**4-(3'-Trifluoromethylphenyl)-amino-6,7-dimethoxyquinazoline (HI-P218)**  
The yield 85.61%; m.p. 242.0–245.0 °C.  $^1H$  NMR(DMSO- $d_6$ ):  $\delta$  11.09(s, 1H, -NH), 8.67(s, 1H, 2-H), 8.03(s, 1H, 5-H), 7.92–7.43(m, 4H, 2'4'5',6'-H), 7.10(s, 1H, 8-H), 3.81(s, 3H, -OCH<sub>3</sub>), 3.79(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 206.0, 276.0, 349.0 nm.. IR  $\nu_{max}$  (KBr): 3372, 3257, 2935, 1626, 1512, 1380, 1225  $cm^{-1}$ . GC/MS m/z 350( $M^+ + 1$ , 10.5), 249( $M^-$ , 85.5), 173( $M^- - 1$ , 100.0), 332(10.5), 290 (8.8).

**4-(4'-Trifluoromethoxyphenyl)-amino-6,7-dimethoxyquinazoline (HI-P219)**  
The yield 83.14%; m.p. 228.0–230.0 °C.  $^1H$  NMR(DMSO- $d_6$ ):  $\delta$  11.39(s, 1H, -

25

HN), 8.63(s, 1H, 2-H), 8.18(s, 1H, 5-H), 7.63(t, 2H, 3',5'-H) . 7.27(t, 2H, 2', 6'-H).  
 7.15(s, 1H, 8-H), 3.81(s, 3H, -OCH<sub>3</sub>), 3.78(s, 3H, -OCH<sub>3</sub>). UV(MeOH):. 209.0,  
 216.0 , 251.0 , 332.0 nm.. IR(KBr) $\nu_{\max}$ : 3207, 2839, 2762, 1633, 1508, 1480, 1276  
 cm<sup>-1</sup>. GC/MS m/z 366(M<sup>+</sup>+1, 12.50). 365(M<sup>-</sup>, 75.00). 364(M<sup>-</sup>-1, 100.00),  
 5 348(17.50), 319(19), 306(8.00). 207(15.00).

**4-(4'-Fluorophenyl)-amino-6,7-dimethoxyquinazoline(HI-P221)** The yield  
 84.25%:. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>) :  $\delta$  11.19(s, 1H, -HN ). 8.60(s, 1H, 2-H). 8.08(s,  
 1H, 5-H)). 7.50(t, 2H, 3'-H) , 7.13(s, 1H, 8-H), 7.12(t, 2H, 2', 6'-H). 3.79(s, 3H, -  
 10 OCH<sub>3</sub> ), 3.78(s, 3H, -OCH<sub>3</sub> ). UV (MeOH):. 225.0 , 251.0 , 333.0 nm.. IR  
 (KBr) $\nu_{\max}$ : 3205, 3007, 2837, 1633, 1580, 1508, 1470. 1220 cm<sup>-1</sup>. GC/MS m/z  
 300(M<sup>+</sup>+1, 10.76), 299(m<sup>-</sup>, 76.92), 398(M<sup>-</sup>-1 , 100.00), 282(20.00).. 253(13.08),  
 207(3.80). Found: C, 57.17; H, 4.37; N, 12.47, C<sub>16</sub>H<sub>14</sub>FN<sub>3</sub>O<sub>2</sub>.HCl requires C.  
 57.31; H, 4.48; N, 12.54%.

15

**4-(4'-Trifluoromethylphenyl)-amino-6,7-dimethoxyquinazoline (HI-P223)**  
 The yield 91.70%; m.p. 243.0-245.0 0°C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>) :  $\delta$  11.47(s, 1H, -  
 NH), 8.67(s, 1H, 2-H), 8.23(s, 1H, 5-H), 7.79(d, 2H, J = 8.4 Hz, 3'5'-H). 7.61(d,  
 2H, J = 8.4 Hz, 2'6'-H ), 7.17(s, 1H, 8-H) , 3.82(s, 3H, -OCH<sub>3</sub>), 3.78(s, 3H, -  
 20 OCH<sub>3</sub>). GC/MS m/z 350(M<sup>+</sup>+1, 11.00). 349(M<sup>-</sup>, 65.00), 348(M<sup>-</sup>-1, 100.00),  
 332(18.50), 303(10.00), 207(18.50). Found: C, 53.01; H, 3.94; N, 10.88. C<sub>1</sub>-  
 H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>HCl requires C. 52.98; H, 3.90; N, 10.91%.

**4-(4'-Fluorophenyl)-amino-6,7-dimethoxyquinazoline(HI-P224)** The yield  
 25 88.69%; m.p. 254.0-255.0 0°C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>):  $\delta$  11.16(s, 1H, -HN), 8.67(s,  
 1H, 2-H), 8.09(s, 1H, 5-H), 7.13(s, 1H, 8-H), 7.51-6/94(m, 4H, 2',3',5',6'-H)O,  
 3.80(s, 3H, -OCH<sub>3</sub>), 3.79(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 206.0, 226.0, 251.0, 333.0.  
 343 nm.. IR(KBr) $\nu_{\max}$ : 3437, 3211, 2619, 1637, 1580, 1500, 1448, 1281 cm<sup>-1</sup>.  
 GC/MS m/z (300(M<sup>+</sup>+1, 8.00), 299(M<sup>-</sup>, 68.00), 398(M<sup>-</sup>-1, 100.00), 282(21.60),  
 30 253(25.00), 207 (80.00),. Found: C, 57.25; H, 4.58; N, 12.42. C<sub>16</sub>H<sub>14</sub>FN<sub>3</sub>O<sub>2</sub>.Hcl  
 requires C, 57.31; H, 4.48; N, 12.54%.

**4-(2'-Trifluoromethylphenyl)-amino-6,7-dimethoxyquinazoline(HI-P228).**

The yield 83.57%; m.p. 242.0-245.0 0°C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>):  $\delta$  11.58(s, 1H, -

HN),  $\delta$  8.76(s, 1H, 2-H), 8.25(s, 1H, 5-H), 7.95–7.62(m, 4H, 3', 4', 5', 6'-H), 7.38(s, 1H, 8-H), 4.01(s, 3H, -OCH<sub>3</sub>), 3.00(s, 3H, -OCH<sub>3</sub>). GC/MS  $m/z$  350(M<sup>+</sup>+1, 8.50), 349(M<sup>-</sup>, 32.00), 348(M<sup>-</sup>-1.31.50), 328(18.50), 207(5.0)I, 280(M<sup>+</sup>-CF<sub>3</sub>, 100.00), 264(18.50), 207(32.50). Found: C, 52.71; H, 4.26; N, 10.91%.

5 **4-[4'-benzenesulfanilyl fluoride]-amino-6,7-dimethoxyquinazoline (HI-P232)**

Yield 84.02%; m.p. 228.0–230.0 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>):  $\delta$  11.62(s, 1H, -NH), 8.78(s, 1H, 2-H), 8.29(s, 1H, 5-H), 8.12–8.02(m, 4H, 2'', 3'', 5'', 6''-H), 7.21(s, 1H, 8-H), 3.86(s, 3H, -OCH<sub>3</sub>), 3.81(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 208.0, 215.0, 253.0, 278.0, 338.0 nm.. IR(KBr) $\nu_{\max}$ : 3440, 3277, 2571, 1635, 1580, 1516, 1435, 1209  
10 cm<sup>-1</sup>. GC/MS  $m/z$ : 281(43.00), 253(12.00), 207(100.00). Found: C, 48.13; H, 3.73; N, 10.53. C<sub>16</sub>H<sub>14</sub>FN<sub>3</sub>O<sub>4</sub>S.HCl requires: C, 48.12; H, 3.76; N, 10.53%.

**4-(2'-Fluorophenyl)-amino-6,7-dimethoxyquinazoline(HI-P264)** Yield

73.58%; m.p. 233.0–235.0 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>):  $\delta$  11.69(d, 1H, -NH),  
15 8.82(s, 1H, 2-H), 8.37(s, 1H, k 50H), 7.59–7.32(m, 4H 3', 4' 5', 6'-H), 7.41(s, 1H, 8H)O, 4.02(s, 3H, -OCH<sub>3</sub>), 4.01(s, 3H, -OCH<sub>3</sub>). UV(MeOH): 204.0, 226.0, 248.0, 330.0 nm. IR(KBr) $\nu_{\max}$ : 3454, 3032, 2638, 1630, 1589, 1514, 1430, 1291 cm<sup>-1</sup>. GC/MS  $m/z$  300(M<sup>+</sup>=1, 7.00), 299(M<sup>-</sup>.38.00), 298(M<sup>-</sup>-1.22.00), 280(M<sup>+</sup>F, 100.00), 264(15.00), 207(35.00). Found: C, 57.12; H, 4.57; N, 12.45.  
20 C<sub>16</sub>H<sub>14</sub>FN<sub>3</sub>O<sub>2</sub>.HCl requires: C, 57.31; H, 4.48; N, 12.54%.

**4-{4'-[2''-(4'''-Aminophenyl)-hexafluoropropyl]phenyl}-amino-6,7-dimethoxyquinazoline(HI-P352)** Yield, 80.41%, m.p. 280.0–282.0 °C. <sup>1</sup>H

NMR(DMSO-d<sub>6</sub>):  $\delta$  11.87(s, 1H, -NH), 8.91(s, 1H, 2-H)I, 8.55–7.18(m, 10H, 5, 8,  
25 2', 3', 5', 6', 2''', 3''', 5''', 6'''-H), 4.05(s, 3H, -OCH<sub>3</sub>), 4.00(s, 3H, -OCH<sub>3</sub>). <sup>19</sup>F NMR(DMSO-d<sub>6</sub>): 128.76. Found: C, 50.33; H, 3.87; N, 9.57. C<sub>25</sub>H<sub>20</sub>F<sub>6</sub>N<sub>4</sub>O<sub>2</sub>.2HCl requires: C, 50.50; H, 3.70; N, 9.42%

**4-{3'-[2''-(3'''-Aminophenyl)-hexafluoropropyl]phenyl}-amino-6,7-dimethoxyquinazoline(HI-P353)** Yield, 83.11%, m.p. 292.0–284.0 °C. <sup>1</sup>H

NMR(DMSO-d<sub>6</sub>):  $\delta$  11.68(s, 1H, -NH). 8.81(s, 1H, 2-H). 8.44–7.09(m, 10H, 5, 8,  
30 2', 4', 5', 6', 2''', 4''', 5''', 6'''-H). 4.00(s, 3H, -OCH<sub>3</sub>). 3.97(s, 3H, -OCH<sub>3</sub>). <sup>19</sup>F NMR(DMSO-d<sub>6</sub>): 129.21. Found: C, 53.96; H, 3.93; N, 9.77. C<sub>25</sub>H<sub>20</sub>F<sub>6</sub>N<sub>4</sub>O<sub>2</sub>.HCl requires: C, 53.76; H, 3.76; N, 10.03%

**4-(3'-Trifluoromethoxyphenyl)-amino-6,7-dimethoxyquinazoline (HI-P364)**

Yield. 83.25%. m.p. 233.0–235.0°C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.65(s, 1H, -NH), 8.88(s, 1H, 2-H), 8.41(s, 1H, 5-H), 7.86–7.29(m, 4H, 2', 4', 5', 6' -H). 7.36(s, 1H, 8-H), 4.02(s, 3H, -OCH<sub>3</sub>). 3.98(s, 3H, -OCH<sub>3</sub>). <sup>19</sup>F NMR(DMSO-d<sub>6</sub>): 135.37.

- 5 GC/MS m/z: 366(M<sup>+</sup>+1, 11.0), 365(M<sup>+</sup>, 67.0), 364(M<sup>+</sup>-1, 100.0). Found: C, 50.93; H, 3.75; N, 10.61. C<sub>17</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub>.HCl requires: C, 50.97; H, 3.74; N, 10.47%.

**4-(2'-Trifluoromethoxyphenyl)-amino-6,7-dimethoxyquinazoline (HI-P365)**

Yield. 77.85%. m.p. 235.0–237.0°C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.68(s, 1H, -NH), 8.80(s, 1H, 2-H), 8.32(s, 1H, 5-H), 7.64–7.53(m, 4H, 3', 4', 5', 6' -H). 7.40(s, 1H, 8-H), 3.99(s, 6H, -OCH<sub>3</sub>). <sup>19</sup>F NMR(DMSO-d<sub>6</sub>): 135.71. GC/MS m/z: 366(M<sup>+</sup>+1, 2.0), 365(M<sup>+</sup>, 15.0), 364(M<sup>+</sup>-1, 4.0), 281(21.0), 280(M<sup>+</sup>-OCF<sub>3</sub>, 100). Found: C, 50.83; H, 3.79; N, 10.52. C<sub>17</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub>.HCl requires: C, 50.87; H, 3.74; N, 10.47%.

- 15 **4-(3', 5'-Ditrifluoromethylphenyl)-amino-6, 7-dimethoxyquinazoline (HI-P366)** Yield. 82.88% m.p. 270.0–272.0°C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.87(s, 1H, -NH), 8.97(s, 1H, 2-H), 8.60(s, 2H, 2', 6'-H), 8.43(s, 1H, 5-H), 7.98(s, 1H, 4'-H), 7.35(s, 1H, 8-H), 4.03(s, 3H, -OCH<sub>3</sub>). 3.99(s, 3H, -OCH<sub>3</sub>). <sup>19</sup>F NMR (DMSO-d<sub>6</sub>): XX GC/MS m/z: 418(M<sup>+</sup>+1, 19.0), 417(M<sup>+</sup>, 100.0), 416(M<sup>+</sup>-1, 73.0), 398(M<sup>+</sup>-F, 16.0), 398(M<sup>+</sup>-F, 16.0), 348(M<sup>+</sup>-CF<sub>3</sub>, 16.0). Found: C, 47.78; H, 3.20; N, 9.26. C<sub>18</sub>H<sub>13</sub>F<sub>6</sub>N<sub>3</sub>O<sub>2</sub>.HCl requires: C, 47.68; H, 3.09; N, 9.27%.

- 20 **4-(4'-Hydroxyl-3'-fluorophenyl)-amino-6,7-dimethoxyquinazoline (HI-P369)** Yield. 84.28%. m.p. 268.0–270.0°C <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.36(s, 1H, -NH), 10.13(s, 1H, -OH), 8.80(s, 1H, 2-H), 8.30(s, 1H, 5-H), 7.60–7.02(m, 3H, 2', 5', 6'-H), 7.31(s, 1H, 8-H), 3.99(s, 3H, -OCH<sub>3</sub>), 3.97(s, 3H, -OCH<sub>3</sub>). <sup>19</sup>F NMR(DMSO-d<sub>6</sub>): δ 57.38. Found: C, 54.90; H, 4.28; N, 11.91. C<sub>16</sub>H<sub>14</sub>FN<sub>3</sub>O<sub>3</sub>.HCl requires C, 54.70; H, 4.27; N, 11.97%.

- 30 **4-(4'-Hydroxyl-3',5'-difluorophenyl)-amino-6,7-dimethoxy-quinazoline (HI-P408)** Yield. 83.15%, m.p. 228.0–230.0 °C. <sup>1</sup>H NMR(DMSO-d<sub>6</sub>): δ 11.46(s, 1H, -NH), 10.39(s, 1H, 2-H), 8.36(s, 1H, 5-H), 7.56, 7.54 (s, s, 2H, 2', 6'-H), 7.33(s, 1H, 8-H), 4.00(s, 3H, -OCH<sub>3</sub>), 3.98(s, 3H, -OCH<sub>3</sub>). <sup>19</sup>F NMR(DMSO-d<sub>6</sub>): δ 60.25, 60.22. Found: C, 52.04; H, 4.17; N, 11.10. C<sub>16</sub>H<sub>13</sub>F<sub>2</sub>N<sub>3</sub>O<sub>3</sub>.HCl. requires C, 52.03; H, 3.79; N, 11.38%.



**Example 7****Anti-Tumor Activities of Specific Quinazoline Compounds**

5                   The cytotoxicity of the substituted quinazoline derivative compounds against a variety of human tumor cells was evaluated. The relative importance of particular substituent groups on the compounds was also studied. The substituted quinazoline derivative compounds, prepared as described above, were tested, along  
10                   with DMSO as a control.

**Cytotoxicity Assay**

                  The cytotoxicity assay of various compounds against human tumor cell lines was performed using the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl  
15                   tetrazolium bromide) assay (Boehringer Mannheim Corp., Indianapolis, IN). Briefly, exponentially growing tumor cells were seeded into a 96-well plate at a density of  $2.5 \times 10^4$  cells/well and incubated for 36 hours at 37°C prior to drug exposure. On the day of treatment, culture medium was carefully aspirated from the wells and replaced with fresh medium containing the quinazoline compounds at  
20                   concentrations ranging from 0.1 to 250  $\mu$ M. Triplicate wells were used for each treatment.

                  Human cell lines were obtained from American Type Culture Collection (Rockville, MD) and maintained as a continuous cell line in Dulbecco's modified Eagles' medium supplemented with 10% fetal bovine serum and antibiotics. Cells  
25                   used in this study include human leukemia cells (NALM-6 and MOLT-3), human breast cancer cells (BR20), human prostate cancer cells (PC3), and human brain tumor cells (U373).

                  The cells were incubated with the various compounds for 24-36 hours at 37°C in a humidified 5% CO<sub>2</sub> atmosphere. To each well, 10  $\mu$ l of MTT (0.5 mg/ml  
30                   final concentration) was added and the plates were incubated at 37°C for 4 hours to allow MTT to form formazan crystals by reacting with metabolically active cells. The formazan crystals were solubilized overnight at 37°C in a solution containing 10% SDS in 0.01 M HCl. The absorbance of each well was measured in a microplate reader (Labsystems) at 540 nm and a reference wavelength of 690 nm.  
35                   To translate the OD<sub>540</sub> values into the number of live cells in each well, the OD<sub>540</sub> values were compared to those on standard OD<sub>540</sub> - versus - cell number curves

generated for each cell line. The percent survival was calculated using the formula:

$$\% \text{ Survival} = \frac{\text{live cell number [test]}}{\text{live cell number [control]}} \times 100$$

The IC<sub>50</sub> values were calculated by non-linear regression analysis.

5

### Detection of Apoptosis

The demonstration of apoptosis was performed by the *in situ* nick-end-labeling method using ApopTag *in situ* detection kit (Oncor, Gaithersburg, MD) according to the manufacturer's recommendations. Exponentially growing cells  
10 were seeded in 6-well tissue culture plates at a density of 50x10<sup>4</sup> cells/well and cultured for 36 hours at 37°C in a humidified 5% CO<sub>2</sub> atmosphere. The supernatant culture medium was carefully aspirated and replaced with fresh medium containing unconjugated EGF or EGF-P154 at a concentration of 10, 25, or 50 µg/ml. After a 36 hour incubation at 37°C in a humidified 5% CO<sub>2</sub>  
15 incubator, the supernatants were carefully aspirated and the cells were treated for 1–2 minutes with 0.1% trypsin. The detached cells were collected into a 15 ml centrifuge tube, washed with medium and pelleted by centrifugation at 1000 rpm for 5 minutes. Cells were resuspended in 50 µl of PBS, transferred to poly-L-lysine coated coverslips and allowed to attach for 15 minutes. The cells were  
20 washed once with PBS and incubated with equilibration buffer for 10 minutes at room temperature.

After removal of the equilibration buffer, cells were incubated for 1 hour at 37°C with the reaction mixture containing terminal deoxynucleotidyl transferase (TdT) and digoxigenin-11-UTP for labeling of exposed 3'-hydroxyl ends of  
25 fragmented nuclear DNA. The cells were washed with PBS and incubated with anti-digoxigenin antibody conjugated to FITC for 1 hour at room temperature to detect the incorporated dUTP. After washing the cells with PBS, the coverslips were mounted onto slides with Vectashield containing propidium iodide (Vector Labs, Burlingame, CA) and viewed with a confocal laser scanning microscope.  
30 Non-apoptotic cells do not incorporate significant amounts of dUTP due to lack of exposed 3'-hydroxyl ends, and consequently have much less fluorescence than apoptotic cells which have an abundance of exposed 3'-hydroxyl ends. In control reactions, the TdT enzyme was omitted from the reaction mixture.

**Results:**

The cytotoxicity results for each tested group of compounds is shown in Tables 1-5 below:

**Table 1**

- 5      **Cytotoxic Activity of Bromo Substituted Quinazoline Compounds against Leukemic (NALM-6 & MOLT-3) and Breast Cancer (BT-20)**

Drug	NALM-6 IC50 ( $\mu$ M)	MOLT-3 IC50 ( $\mu$ M)	BT20 IC50 ( $\mu$ M)
HI-P79	142.1	194.9	201.5
HI-P88	>250	>250	>250
HI-P97	>250	>250	26.1
HI-P111	200.6	>250	>250
HI-P154	12.5	9.1	>250
HI-P160	135.2	240.7	25.5
HI-P164	>250	>250	39.2
HI-P190	>250	>250	>250
HI-P210	>250	>250	>250
HI-P211	>250	>250	>250
HI-P212	52.7	54.5	>250
HI-P214	>250	>250	>250
HI-P222	34.0	48.3	>250
HI-P234	>250	>250	>250
HI-P241	>250	>250	>250
HI-P258	>250	>250	>250
HI-P260	32.4	51.3	82.1
HI-P261	72.6	148.5	218.6
HI-P262	>250	>250	>250

**Table 2**

- 10      **Cytotoxic Activity of Chloro Substituted Quinazoline Compounds against Leukemic (NALM-6 & MOLT-3) and Breast Cancer (BT-20)**

Drug	NALM-6 IC50 ( $\mu$ m)	MOLT-3 IC50 ( $\mu$ m)	BT20 IC50 ( $\mu$ m)
HI-P87	95.9	>104.6	>250
HI-P93	>250	>250	>250
HI-P189	>250	>250	>250
HI-P197	39.3	68.0	136.9
HI-P239	29.6	28.7	25.7
HI-P246	>250	>250	>250
HI-P268	215.2	227.4	121.5
HI-P269	>250	>250	>250
HI-P415	67.9	>250	38.1

**Table 3**

**Cytotoxic Activity of Iodide Substituted Quinazoline Compounds against Leukemic (NALM-6 & MOLT-3), Breast Cancer (BT-20) and Brain Tumor (U373) cells**

5

Drug	NALM-6 IC50 ( $\mu$ M)	MOLT-3 IC50 ( $\mu$ M)	BT20 IC50 ( $\mu$ M)	U373 IC50 ( $\mu$ M)
HI-P270	>250	78.9	>250	>250
HI-P271	6.1	9.6	>250	>250
HI-P294	>250	>250	>250	>250
HI-P299	15.4	60.1	>250	>250
HI-P300	58.0	59.1	72.6	116.2

**Table 4**

**Cytotoxic Activity of OH Substituted Quinazokline Compounds against Leukemic (NALM-6 & MOLT-3), Breast Cancer (BT-20) and Brain Tumor (U373) cells**

10

Drug	NALM-6 IC50 ( $\mu$ M)	MOLT-3 IC50 ( $\mu$ M)	BT20 IC50 ( $\mu$ M)	U373 IC50 ( $\mu$ M)
HI-P93	>250	>250	>250	>250
HI-P97	>250	>250	26.1	161.2
HI-P131	32.1	38.6	>250	>250
HI-P154	12.5	9.1	>250	167.4
HI-P189	>250	>250	>250	>250
HI-P190	>250	>250	>250	>250
HI-P192	>250	>250	>250	>250
HI-P197	68.5	63.8	71.5	>250
HI-P294	>250	>250	>250	>250
HI-P299	66.3	51.2	>250	>250

**Table 5****Cytotoxic activity of fluoro-substituted dimethoxy quinazolines on cancer cells.**

Compound	NALM-6 IC50 ( $\mu$ M)	MOLT-3 IC50 ( $\mu$ M)	U373 IC50 ( $\mu$ M)	BT20 IC50 ( $\mu$ M)	PC3 IC50 ( $\mu$ M)
HI-P144	28.1 $\pm$ 2.6	24.9 $\pm$ 3.7	49.5 $\pm$ 11.3	63.4 $\pm$ 5.5	>250
HI-P214	>250	>250	>250	>250	>250
HI-P218	37.0 $\pm$ 5.8	33.2 $\pm$ 3.3	29.9 $\pm$ 7.3	37.62 $\pm$ 5.2	126.1 $\pm$ 5.8
HI-P219	22.3 $\pm$ 3.0	41.3 $\pm$ 4.4	83.6 $\pm$ 6.5	44.2 $\pm$ 10.9	58.3 $\pm$ 3.2
HI-P221	100.5 $\pm$ 4.8	98.73 $\pm$ 3.8	28.8 $\pm$ 12.7	30.67 $\pm$ 7.9	>250
HI-P223	39.5 $\pm$ 8.0	40.8 $\pm$ 15.1	32.1 $\pm$ 3.9	27.56 $\pm$ 8.6	>250
HI-P224	20.15 $\pm$ 8.1	23.3 $\pm$ 7.7	22.4 $\pm$ 5.9	58.33 $\pm$ 5.8	>250
HI-P228	57.3 $\pm$ 24.8	237.1 $\pm$ 4.8	>250	>250	>250
HI-P232	41.4 $\pm$ 6.9	43.6 $\pm$ 2.3	207.7 $\pm$ 18.1	70.54 $\pm$ 8.2	88.9 $\pm$ 17.2
HI-P264	47.0 $\pm$ 19.5	70.9 $\pm$ 17.3	53.3 $\pm$ 6.7	33.33 $\pm$ 7.5	>250
HI-P352	7.1 $\pm$ 1.8	21.8 $\pm$ 1.7	65.5 $\pm$ 11.2	50.3 $\pm$ 14.8	72.6 $\pm$ 2.5
HI-P353	6.1 $\pm$ 1.4	17.4 $\pm$ 1.5	14.5 $\pm$ 7.6	14.1 $\pm$ 3.3	64.9 $\pm$ 11.9
HI-P364	7.9 $\pm$ 1.9	25.3 $\pm$ 9.1	27.7 $\pm$ 1.2	40.1 $\pm$ 8.6	>250
HI-P365	86.5 $\pm$ 3.4	110.7 $\pm$ 7.5	>250	>250	>250
HI-P366	52.8 $\pm$ 14.0	137.2 $\pm$ 10.3	55.5 $\pm$ 13.2	61.7 $\pm$ 12.1	>250
HI-P369	>250	>250	>250	>250	>250
HI-P408	116.3 $\pm$ 17.8	228.5 $\pm$ 20.8	>250	>250	>250

5           The compounds were tested for activity against various cancer cells. For example, NALM-6 cells were incubated with HI-P144, HI-P214, HI-P221, HI-P224, HI-P258, HI-P264, HI-P218, HI-P223, HI-P228, HI-P366, HI-P367, HI-P219, HI-P352, HI-P353, HI-P364 or HI-P365 for 24 hours in 96-well plates and cell survival was determined by MTT assay. The data points represent the means  
10   ( $\pm$ SE) values from 3 independent experiments.

BT-20 breast cancer cells were incubated with HI-P144, HI-214, HI-P221, HI-P224, HI-P258, HI-P264, HI-P218, HI-P223, HI-P228, HI-P366, HI-P367, HI-P219, HI-P352, HI-P353, HI-P364, or HI-P365 for 24 hours in 96-well plates and cell survival was determined by MTT assay. The data points represent the mean  
15   ( $\pm$  SE) values from 3 independent experiments.

Apoptosis was induced by the compounds. The cells were incubated with HI-P353 or HI-P219 for 24 hours, fixed, permeabilized, and visualized for DNA degradation in a TUNEL assay using digoxigenin-UTP-labeling kit. In the color photographs, red fluorescence represents nuclei stained with propidium iodide.  
20   Green or yellow (i.e., superimposed red plus green) represents the apoptotic nuclei.

Shown are control NALM-6 (Figure 3A) and BT-20 (Figure 3B) cells; HI-P353 treated NALM (Figure 3D) and BT-20 cells (Figure 3E); and control (Figure 3C) and HI-P219 treated PC3 cells (Figure 3F).

5

### Example 8

#### Pharmacokinetic Studies:

In pharmacokinetic studies, mice were injected either intravenously (i.v.) via the tail vein or intraperitoneally (i.p.) with a bolus dose of 300 µg/mouse (~12.5 mg/kg = 34 µmols/kg) of HI-P131. Blood samples were obtained from the ocular venous plexus by retroorbital venupuncture prior to and at 3 minutes, 5 minutes, 10 minutes, 15 minutes, 30 minutes, 45 minutes and 1 hour, 2 hours, 4 hours, and 8 hours after administration of HI-P131. All collected blood samples were heparinized and centrifuged at 7,000 xg for 10 minutes in a microcentrifuge to obtain plasma. The plasma samples were stored at -20°C until analysis. Aliquots of plasma were used for extraction and HPLC analysis. Pharmacokinetic modeling and pharmacokinetic parameter calculations were carried out using the pharmacokinetics software, WinNonline Program, Version 1.1. (Scientific Consulting Inc., Cary, NC). Concentration data were weighted by 1/concentration. An appropriate pharmacokinetic model was chosen on the basis of lowest weighted squared residuals, lowest Schwartz criterion (SC), lowest Akaike's Information Criterion (AIC) value, lowest standard errors of the fitted parameters, and dispersion of the residuals. The elimination half-life was estimated by linear regression analysis of the terminal phase of the plasma concentration profile. The area under the concentration time curve (AUC) was calculated by the trapezoidal rule between first (0 h) and last sampling time plus C/k, where C is the concentration of last sampling and k is the elimination rate constant. Systemic clearance (CL) was determined by dividing the dose by the AUC. The apparent volume of distribution at steady-state was calculated using the following equation,  $V_{ss} = \text{Dose} \cdot \text{AUMC} / (\text{AUC})^2$ . Bioavailability (F) was estimated using the equation  $F(\%) = \text{AUC}_{ip} \times \text{Dose}_{iv} / \text{AUC}_{iv} \times \text{Dose}_{ip}$ .

#### **HPLC Analysis of Plasma HI-P131 Levels:**

A highly sensitive quantitative HPLC detection method (Chen et. al., 1998, *J. Chromatography B (Biomedical sciences)*, in press) was used to determine the

pharmacokinetics of HI-P131. In brief, the HPLC system consisted of a Hewlett Packard (HP) series 1100 equipped with an automated electronic degasser, a quaternary pump, an autosampler, an automatic thermostatic column compartment, diode array detector and a computer with a Chemstation software program for data analysis. A 250 x 4 mm Lichrospher 100, RP-18 (5  $\mu$ m) analytical column and a 4 x 4 mm Lichrospher 100, RP-18 (5  $\mu$ m) guard column were obtained from Hewlett Packard Inc. (San Fernando, CA). Acetonitrile/water containing 0.1% of trifluoroacetic acid (TFA) and 0.1% triethylamine (TEA) (28:72, v/v) was used as the mobile phase. The wavelength of detection was set at 340 nm. Peak width, response time and slit were set at >0.03 minutes, 0.5 seconds and 8 nm, respectively.

For determination of HI-P131 levels, 10  $\mu$ L of internal standard HI-P154 (50  $\mu$ M) was added to a 100  $\mu$ L plasma sample. For extraction, 7 ml chloroform was then added to the plasma sample, and the mixture was vortexed thoroughly for 3 minutes. Following centrifugation (300 xg, 5 minutes), the aqueous layer was frozen using acetone/dry ice and the organic phase was transferred into a clean test tube. The chloroform extracts were dried under a slow steady stream of nitrogen. The residue was reconstituted in 100  $\mu$ L of methanol: water (9:1) and 50  $\mu$ L aliquot of this solution was used for HPLC analysis. Under the described chromatographic separation conditions, the retention times for HI-P131 and HI-P154 were 5.1 minutes and 9.5 minutes, respectively. At the retention time, HI-P131 and its internal standard HI-P154 were eluted without any interference peaks from the blank plasma.

HI-P131 was not toxic to mice at intraperitoneal single bolus doses ranging from 0.5 mg/kg to 250 mg/kg. None of the 50 mice treated with HI-P131 experienced side effects or died of toxicity during the 30 day observation period. In particular, we observed no hematologic side effects such as neutropenia, lymphopenia, or anemia at the tested dose levels. No histopathologic lesions were found in the organs of HI-P131 treated mice that were selectively killed at 30 days and there was no bone marrow hypoplasia or lymphoid cell depletion in spleen and lymph nodes. Thus, the maximum tolerated dose (MTD) of HI-P131 was not reached at 250 mg/kg. We next examined the pharmacokinetic features of HI-P131 in mice. A two-compartment pharmacokinetic model was fit to the pharmacokinetics data obtained following the intravenous (i.v.) or intraperitoneal (i.p.) administration of a single non-toxic 12.5 mg/kg bolus dose of HI-P131. The

estimated maximum plasma concentrations ( $C_{\max}$ ) of HI-P131 were 85.6  $\mu\text{M}$  after i.v. administration.

### Example 9

#### 5                    Antitumor Activity of Quinazolines *In vivo*

To test the anti-tumor activity of quinazolines *in vivo*, cancer cells were implanted and grown in mice in the presence of quinazoline.

#### 10        **Inhibition of breast cancer cells**

The left hind legs of CB.17 SCID mice were inoculated subcutaneously with  $0.75 \times 10^6$  MDA-MB-231 human breast cancer cells in 0.1 ml PBS. Twenty-four hours after inoculation, the mice were treated with HI-P353 (10 mg/kg/day x 5 days/week, N=7), or HI-P364 (10 mg/kg/day x 5 days/week, N=8), or vehicle (50% DMSO in PBS, N=7) for four weeks. The mice were monitored daily for health status and tumor growth. Measurements were taken on the tumors 3 times a week using a Vernier caliper. Tumor volumes were calculated using the following formula:  $(\text{width})^2 \times (\text{length}/2)$ . Comparisons of the outcomes of the three groups were done using the log-rank test.

20                The data are shown in Figure 10A, and demonstrate that treatment of animals with the quinazolines of the invention (HI-P353 and HI-P364) inhibited the growth of breast cancer cell tumors as compared with untreated controls.

#### **Inhibition of brain tumor cells**

25                An analogous experiment was done implanting brain tumor cells into mice. The right hind legs of CB.17 SCID mice were inoculated subcutaneously with  $1 \times 10^6$  of U373 human glioblastoma cells in 0.1 ml of PBS. Twenty four hours after inoculation, mice were treated with HI-P353 (10 mg/kg/day x 5 days/week, N=7), or HI-P364 (10 mg/kg/day x 5 days/week, N=8), or vehicle (50% DMSO in PBS, N=7) for four weeks. Mice were monitored daily for health status and tumor growth. Tumors were measured 3 times a week using a Vernier caliper. Tumor volumes were calculated using the following formula:  $(\text{width})^2 \times (\text{length}/2)$ . Comparisons of outcome between groups were done using the log-rank test.



The data are shown in Figure 10B and demonstrate that treatment of animals with the quinazolines of the invention (HI-P353 and HI-P364) inhibited the growth of brain tumors as compared with untreated controls.

## 5    **Inhibition of intracranial brain tumors**

The anti-tumor activity of the quinazolines of the invention was also studied with intracranial tumors. Nude mice were first anesthetized with Avertin. Under aseptic conditions in a laminar flow hood, a small hole was drilled at 2 mm to the right of the midline and 2 mm posterior to the bregma. An amount of  $4 \times 10^5$  U87  
10 glioblastoma cells in 10  $\mu$ L of PBS were intracranially implanted using a Hamilton syringe into the right cerebral hemisphere of mice and a stereotaxic apparatus according to the method described in Huang, H.J.S. et al., *J. Biol. Chem.* 272:2927-2935, 1997.

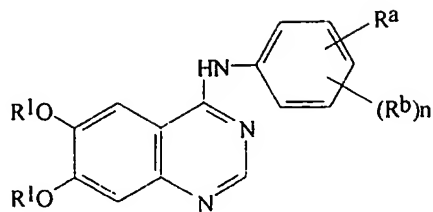
Twenty-four hours after inoculation, mice were treated with HI-P353 (20  
15 mg/kg/day x 10 days, n=10), HI-P364 (20 mg/kg/day x 10 days, n=10), or vehicle (50% DMSO in PBS, n=10). The mice were monitored twice daily for health status.

Figure 10C shows the survival rate of mice inflicted with intracranial tumors. Treatment of mice with quinazolines (HI-P353 and HI-P364) resulted in prolonged  
20 survival as compared with mice treated with vehicle alone.

All publications, patents, and patent documents described herein are incorporated by reference as if fully set forth. The invention described herein may be modified to include alternative embodiments. All such obvious alternatives are  
25 within the spirit and scope of the invention, as claimed below.

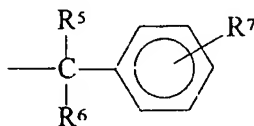
WE CLAIM:

1. A compound of the formula:



wherein:

$R^a$  is iodo,  $(C_1-C_4)$ hydroxyalkyl, methylenedioxy, ethylenedioxy, benzyloxy,  $OCF_3$ ,  $SCF_3$ ,  $SO_3H$ ,  $SO_2F$ ,  $SO_2NR^2R^3$  where  $R^2$  is hydrogen or  $(C_1-C_4)$ alkyl and  $R^3$  is hydrogen,  $(C_1-C_4)$ alkyl, or phenyl,  $NR^2R^4$  where  $R^2$  is hydrogen or  $(C_1-C_4)$ alkyl and  $R^4$  is phenyl; or a group of the formula



wherein  $R^5$  and  $R^6$  are each independently, hydrogen,  $(C_1-C_4)$ alkyl, or  $(C_1-C_4)$ perfluoroalkyl, and  $R^7$  is hydrogen, halo, hydroxy,  $(C_1-C_4)$ alkyl,  $(C_1-C_4)$ alkoxy,  $(C_1-C_4)$ hydroxyalkyl, or  $N(R^2)_2$ , where  $R^2$  is hydrogen or  $(C_1-C_4)$ alkyl;

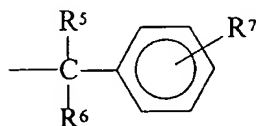
$n$  is an integer of 1-4;

$R^b$  is each, independently, hydrogen, halo, hydroxy, mercapto,  $(C_1-C_4)$ alkyl,  $(C_1-C_4)$ alkoxy,  $(C_1-C_4)$ thioalkyl,  $(C_1-C_4)$ hydroxyalkyl, nitro, cyano, methylenedioxy, ethylenedioxy,  $COCH_3$ ,  $CF_3$ ,  $OCF_3$ ,  $SCF_3$ ,  $COOH$ ,  $SO_3H$ ,  $SO_2F$ , phenyl, or phenyl substituted by a group selected from halo, hydroxy, mercapto,  $(C_1-C_4)$ alkyl,  $(C_1-C_4)$ alkoxy,  $(C_1-C_4)$ thioalkyl,  $(C_1-C_4)$ hydroxyalkyl, amino, nitro, cyano,  $CF_3$ ,  $COOH$ ,  $SO_3H$ ,  $SO_2NR^2R^3$ ,  $SO_2F$  where  $R^2$  is H or  $(C_1-C_4)$ alkyl and  $R^3$  is H,  $(C_1-C_4)$ alkyl, phenyl, or phenyl substituted by a group as defined above; benzyloxy or benzyloxy substituted on the phenyl portion by a group defined above;  $NR^2R^3$  where  $R^2$  is H or  $(C_1-C_4)$ alkyl and  $R^3$  is H,  $(C_1-C_4)$ alkyl, phenyl, or phenyl substituted by a group as defined above; and

$R^1$  is  $(C_1-C_4)$ alkyl or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein the pharmaceutically acceptable salt is an acid addition salt.

3. The compound of claim 1, wherein  $R^1$  is methyl.
4. The compound of claim 3, wherein  $R^a$  is a member selected from the group consisting of I,  $\text{NHC}_6\text{H}_5$ ,  $-\text{OCH}_2\text{CH}_2\text{O}-$ ,  $-\text{OCH}_2\text{O}-$ ,  $\text{OCF}_3$ ,  $\text{SCF}_3$ ,  $\text{CH}_2\text{OH}$ ,  $\text{C}_2\text{H}_4\text{OH}$ ,  $\text{SO}_3\text{H}$ ,  $\text{SO}_2\text{NH}_2$ , and  $\text{SO}_2\text{F}$ .
5. The compound of claim 4, wherein  $R^a$  is I,  $\text{OCF}_3$ , or  $\text{SO}_2\text{F}$ .
6. The compound of claim 5, wherein  $R^a$  is I.
7. The compound of claim 5 wherein  $R^a$  is  $\text{OCF}_3$ .
8. The compound of claim 3, wherein n is 1 and  $R^a$  is a group of the formula



9. The compound of claim 8, wherein  $R^5$  and  $R^6$  are each, independently, H,  $\text{CH}_3$ , or  $\text{CF}_3$ .
10. The compound of claim 9, wherein  $R^5$  and  $R^6$  are  $\text{CF}_3$  and  $R^7$  is  $\text{NH}_2$ .
11. The compound of claim 3, wherein  $R^b$  is at least one member selected from the group consisting of F, Cl, Br, I, OH,  $\text{NH}_2$ ,  $\text{NO}_2$ , CN, COOH,  $\text{CH}_3$  and  $\text{CF}_3$ .
12. The compound of claim 11, wherein  $R^b$  is at least one member selected from the group consisting of F, Cl, Br, OH and  $\text{CF}_3$ .
13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

14. A method of treating tumors in a subject comprising administering to said subject an anti-tumor effective amount of a compound of claim 1.

15. A method of treating leukemia in a subject comprising administering to said subject a compound of claim 1 in an amount effective for inducing apoptosis of leukemia cells.

16. A method of inhibiting cancer cell growth in a subject comprising administering to said subject a cytotoxic effective amount of a compound of claim 1.

17. A method of treating leukemia in a subject comprising administering to said subject a compound selected from the group consisting of:

4-(3',5'-dibromo-4'-methylphenyl)amino-6,7-dimethoxyquinazoline,  
4-(2',4',6'-tribromophenyl)amino-6,7-dimethoxyquinazoline,  
4-(2',3',5',6'-tetrafluoro-4'-bromophenyl)amino-6,7-dimethoxyquinazoline,  
4-(4'-fluorophenyl)amino-6,7-dimethoxyquinazoline,  
4-(3'-fluorophenyl)amino-6,7-dimethoxyquinazoline,  
4-(2'-fluorophenyl)amino-6,7-dimethoxyquinazoline,  
4-(4'-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline,  
4-(2'-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline,  
4-(3',5'-bis-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline,  
and pharmaceutically acceptable acid addition salts thereof.

18. A method of treating breast tumors in a subject comprising administering to said subject a compound selected from the group consisting of

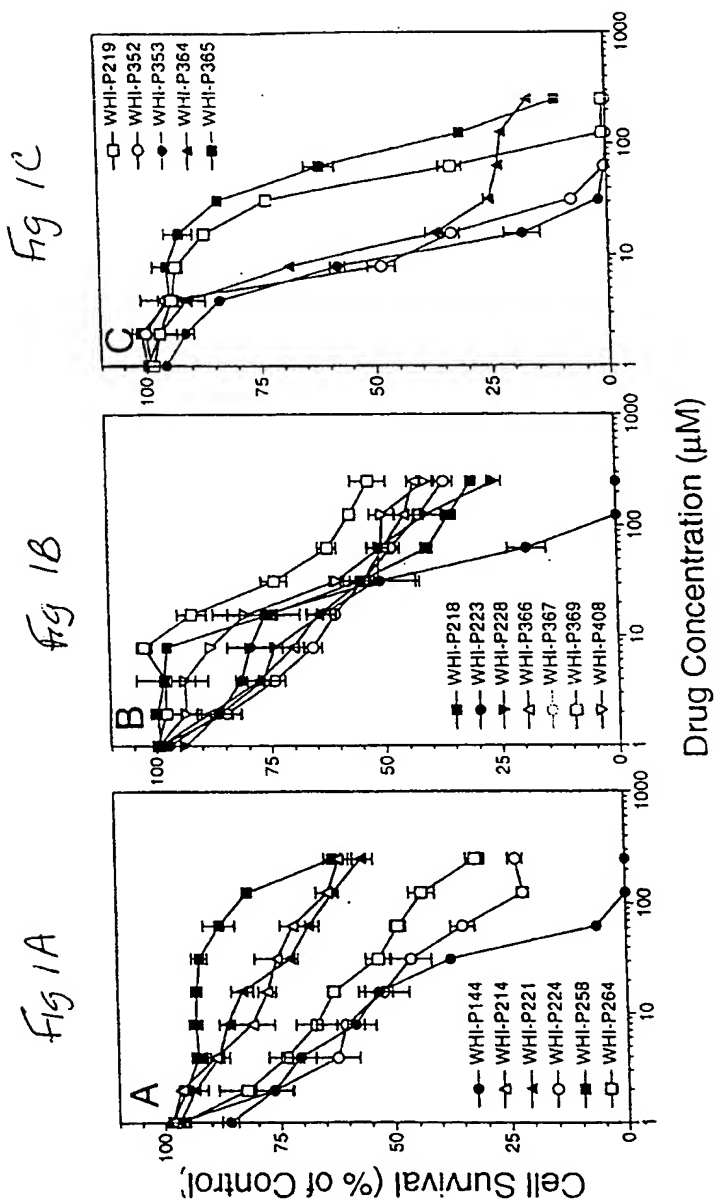
4-(3'-bromophenyl)amino-6,7-dimethoxyquinazoline,  
4-(3',5'-dibromo-4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline,  
4-(3'-chloro-4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline,  
4-(3',5'-bis-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline,  
4-(2',3',5',6'-tetrafluoro-4'-bromophenyl)amino-6,7-dimethoxyquinazoline,  
4-(4'-fluorophenyl)amino-6,7-dimethoxyquinazoline,  
4-(3'-fluorophenyl)amino-6,7-dimethoxyquinazoline,  
4-(2'-fluorophenyl)amino-6,7-dimethoxyquinazoline. and

pharmaceutically acceptable acid addition salts thereof.

19. A method of treating multi-drug resistant leukemia in a subject comprising administering to said subject 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline or a pharmaceutically acceptable salt thereof, in an amount effective for inducing apoptosis of multi-drug resistant leukemia cells.
20. A method of treating multi-drug resistant leukemia in a subject comprising administering to said subject 4-(3'-bromo-4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline or a pharmaceutically acceptable acid addition salt thereof, in an amount effective for inducing apoptosis of multi-drug resistant leukemia cells.
21. The compound 4-(3',5'-dibromo-4'-methylphenyl)amino-6,7-dimethoxyquinazoline or a pharmaceutically acceptable acid addition salt thereof.
22. The compound 4-(2',4',6'-tribromophenyl)amino-6,7-dimethoxyquinazoline or a pharmaceutically acceptable acid addition salt thereof.
23. The compound 4-(2',3',5',6'-tetrafluoro-5'-bromophenyl)amino-6,7-dimethoxyquinazoline or a pharmaceutically acceptable acid addition salt thereof.
24. The compound 4-(4'-fluorophenyl)amino-6,7-dimethoxyquinazoline or a pharmaceutically acceptable acid addition salt thereof.
25. The compound 4-(4'-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline or a pharmaceutically acceptable acid addition salt thereof.
26. The compound 4-(3',5'-bis-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline or a pharmaceutically acceptable acid addition salt thereof.
27. A pharmaceutical composition comprising an effective amount of a compound selected from the group consisting of:  
4-(3',5'-bis-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline.

4-(2',4',6'-tribromophenyl)amino-6,7-dimethoxyquinazoline.  
4-(2',3',5',6'-tetrafluoro-4'-bromophenyl)amino-6,7-  
dimethoxyquinazoline,  
4-(3',5'-dibromo-4'-methylphenyl)amino-6,7-dimethoxyquinazoline.  
4-(4'-fluorophenyl)amino-6,7-dimethoxyquinazoline,  
4-(4'-trifluoromethylphenyl)amino-6,7-dimethoxyquinazoline, and  
pharmaceutically acceptable acid addition salts thereof; and  
a pharmaceutically acceptable carrier or diluent.

# Cytotoxicity of F-dmQ in Leukemic Cells



Cytotoxicity of F-dmQ in Breast Cancer Cells

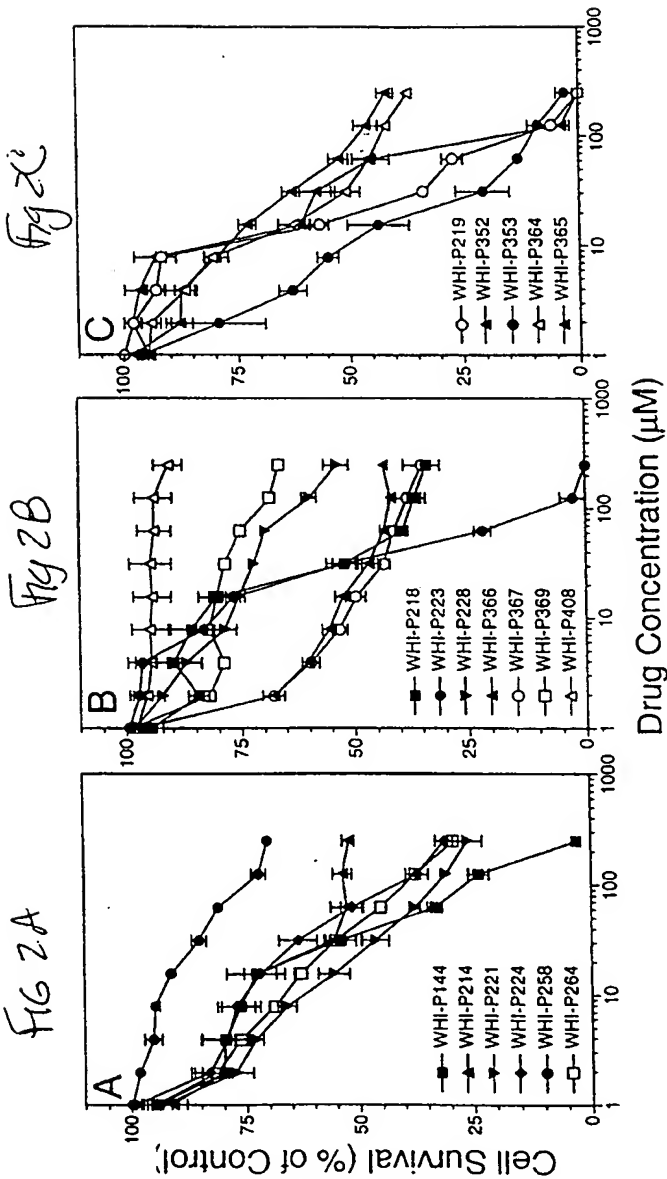




Fig 3A

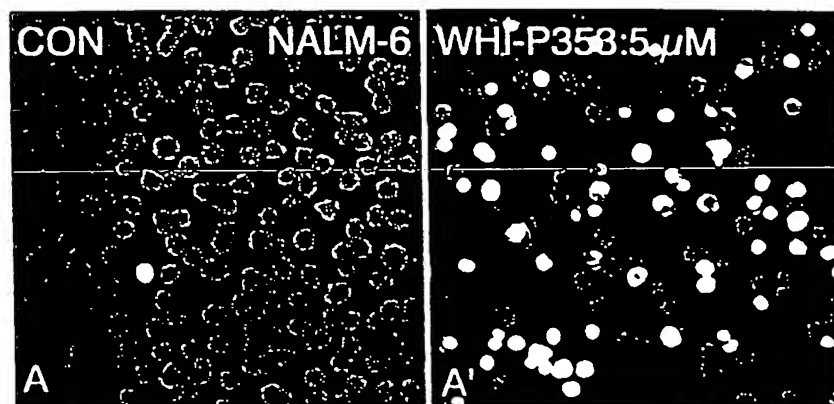


Fig 3B

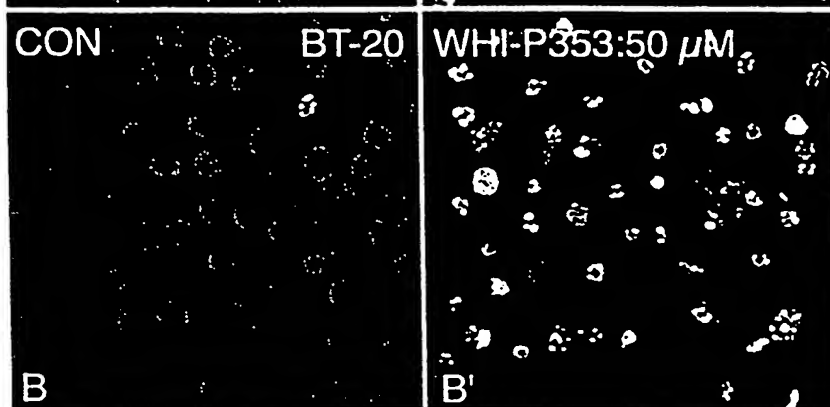


Fig 3C

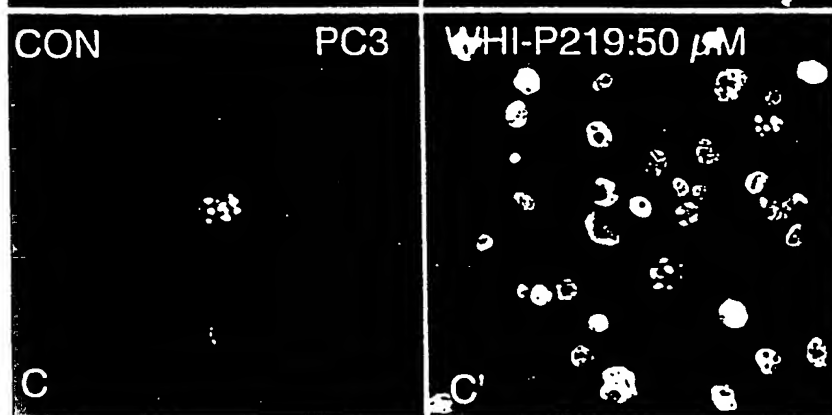
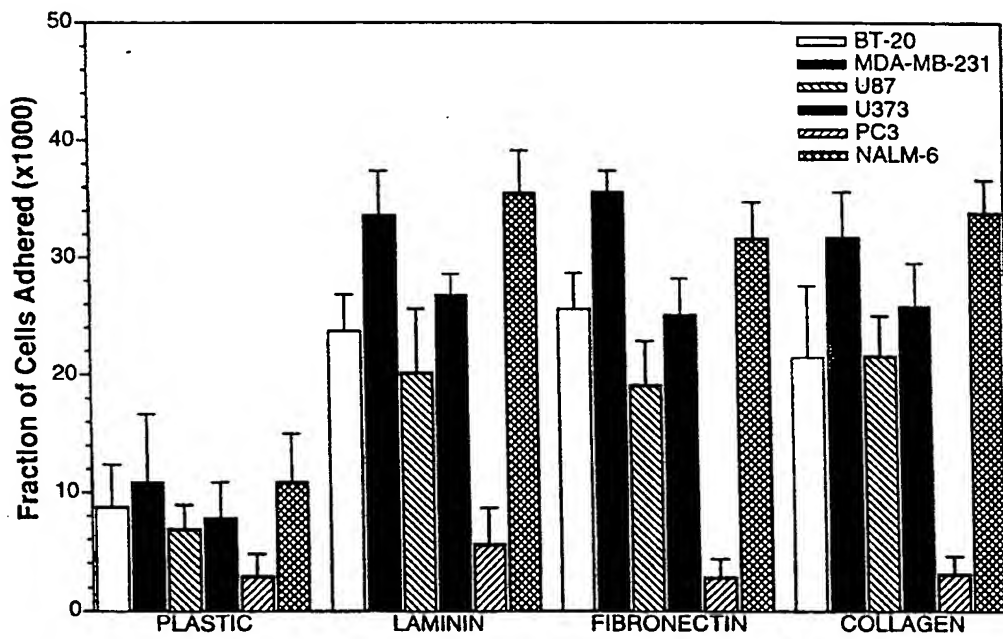


Fig 3D

Fig 3E

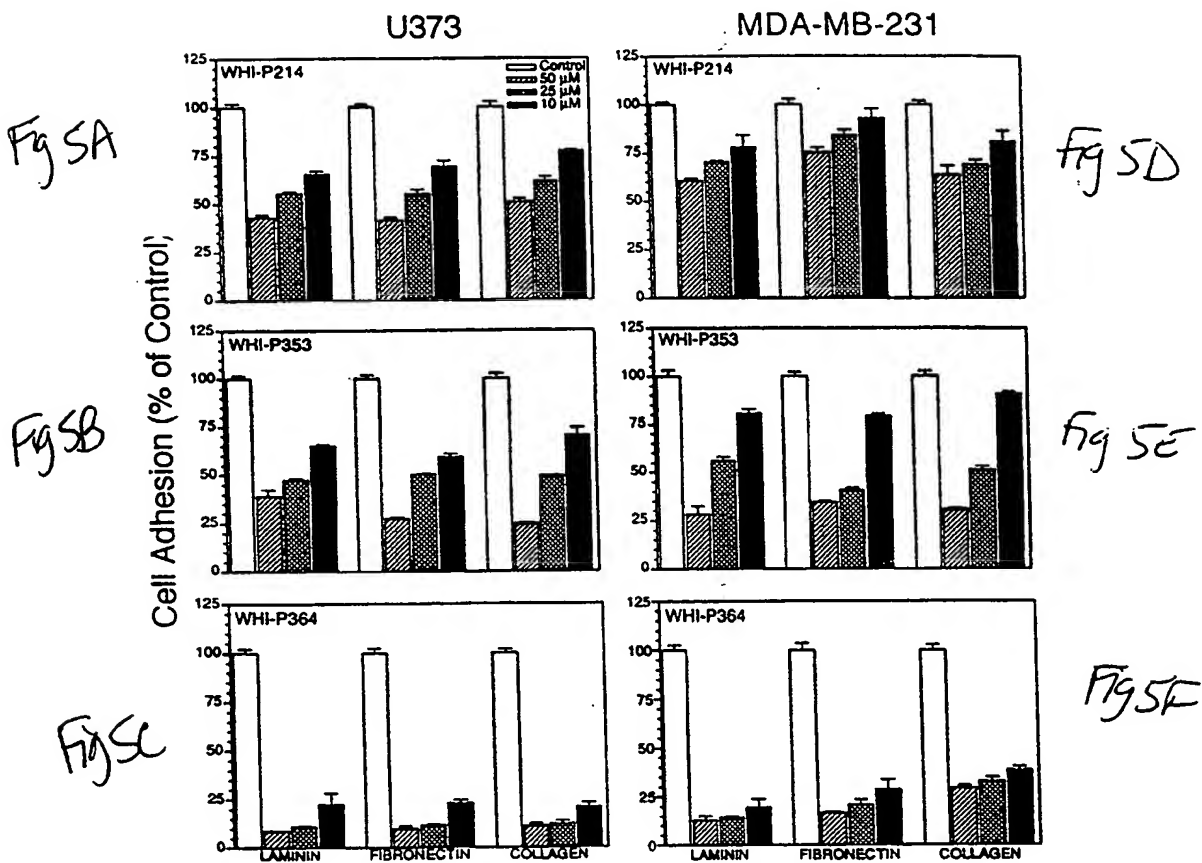
Fig 3F

Figure 4  
ECM proteins promote adhesion



Figures A - F  
F-dmQ inhibit adhesion

Fig 5



Figs 6A-F Edm2 inhibit glioblastoma cell migration

PC,Fluoro.1

WHI-P353:2  $\mu$ M



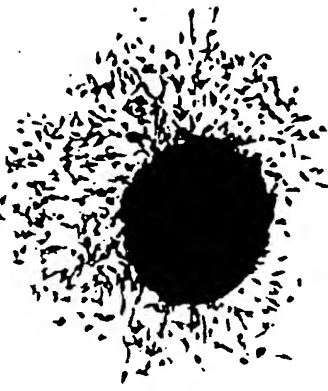
C

WHI-P364:2  $\mu$ M



F

WHI-P353:1  $\mu$ M



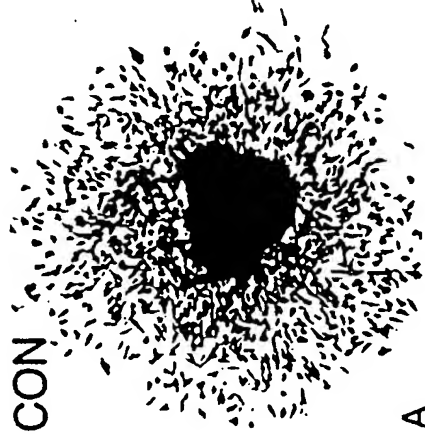
B

WHI-P364:1  $\mu$ M



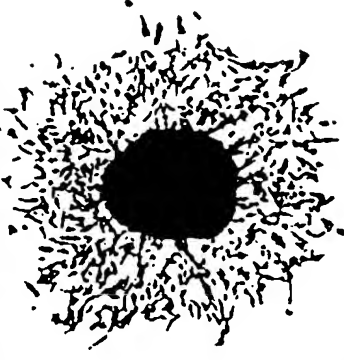
E

CON



A

WHI-P364:0.5  $\mu$ M



D

Fig 6

Fig 7  
ANTI-INVASIVE ACTIVITY OF F-olmQ

Fig 7A

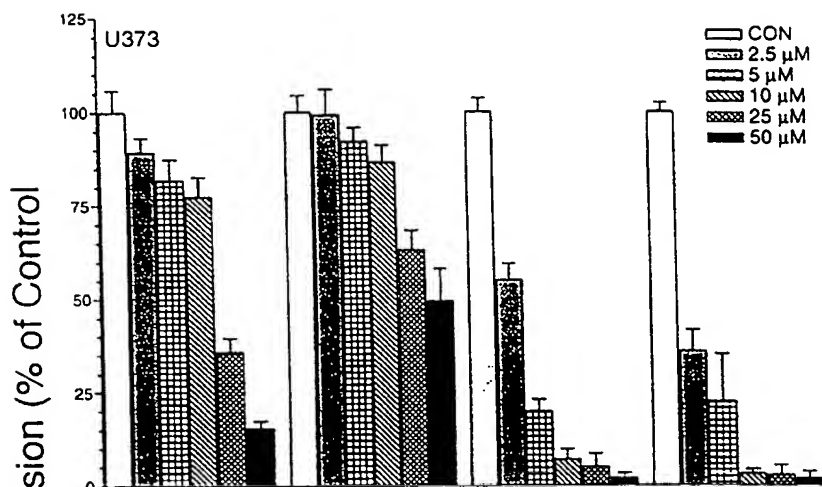


Fig 7B

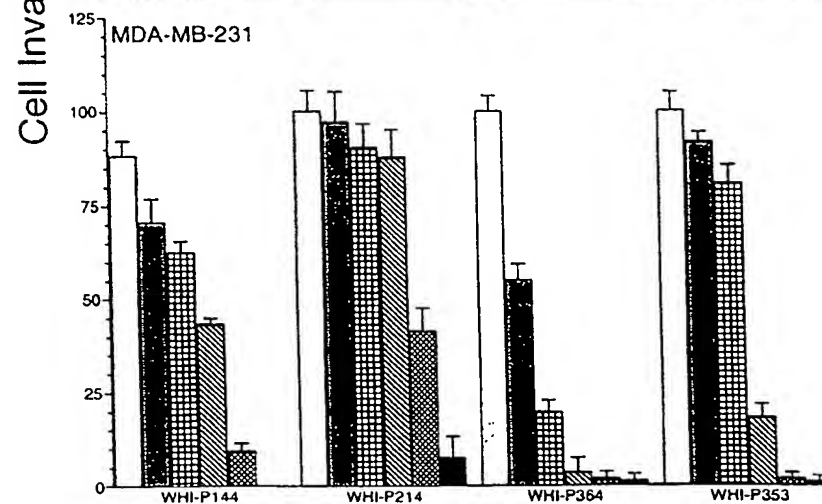


Fig 8

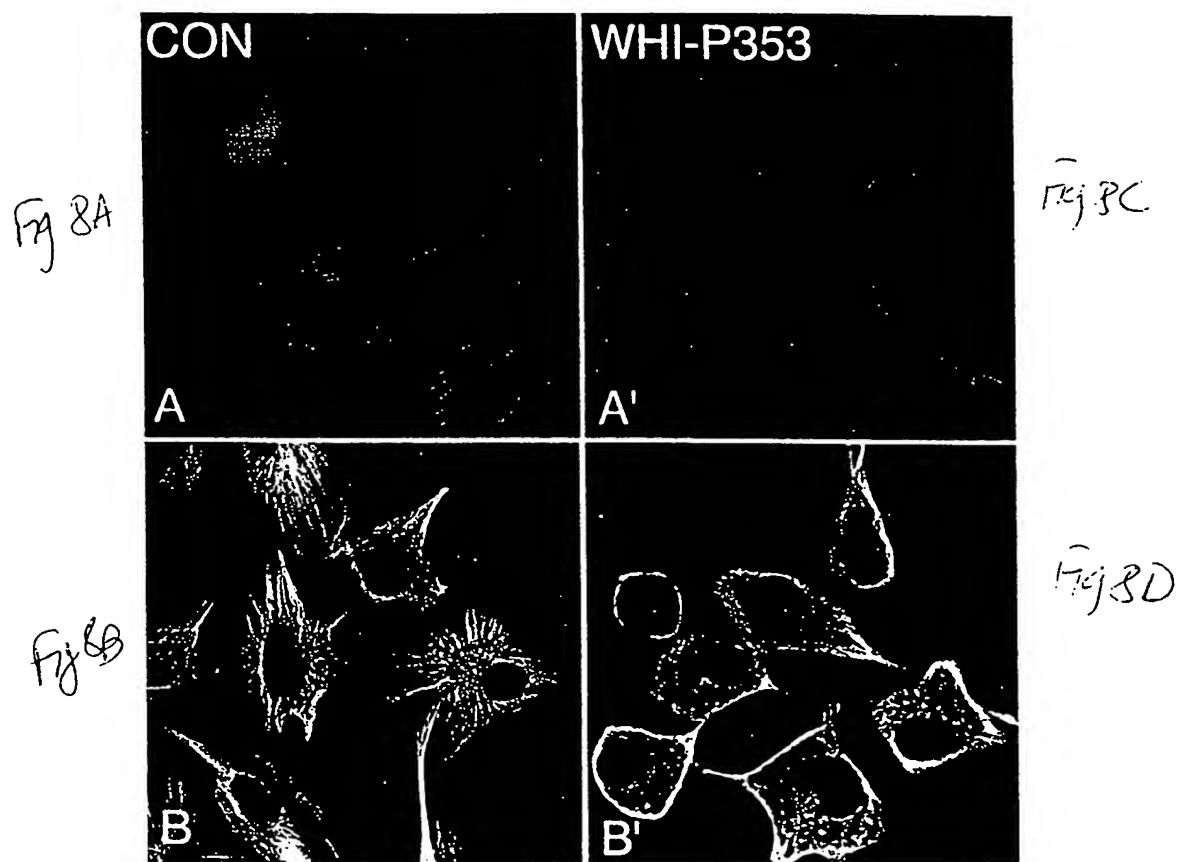
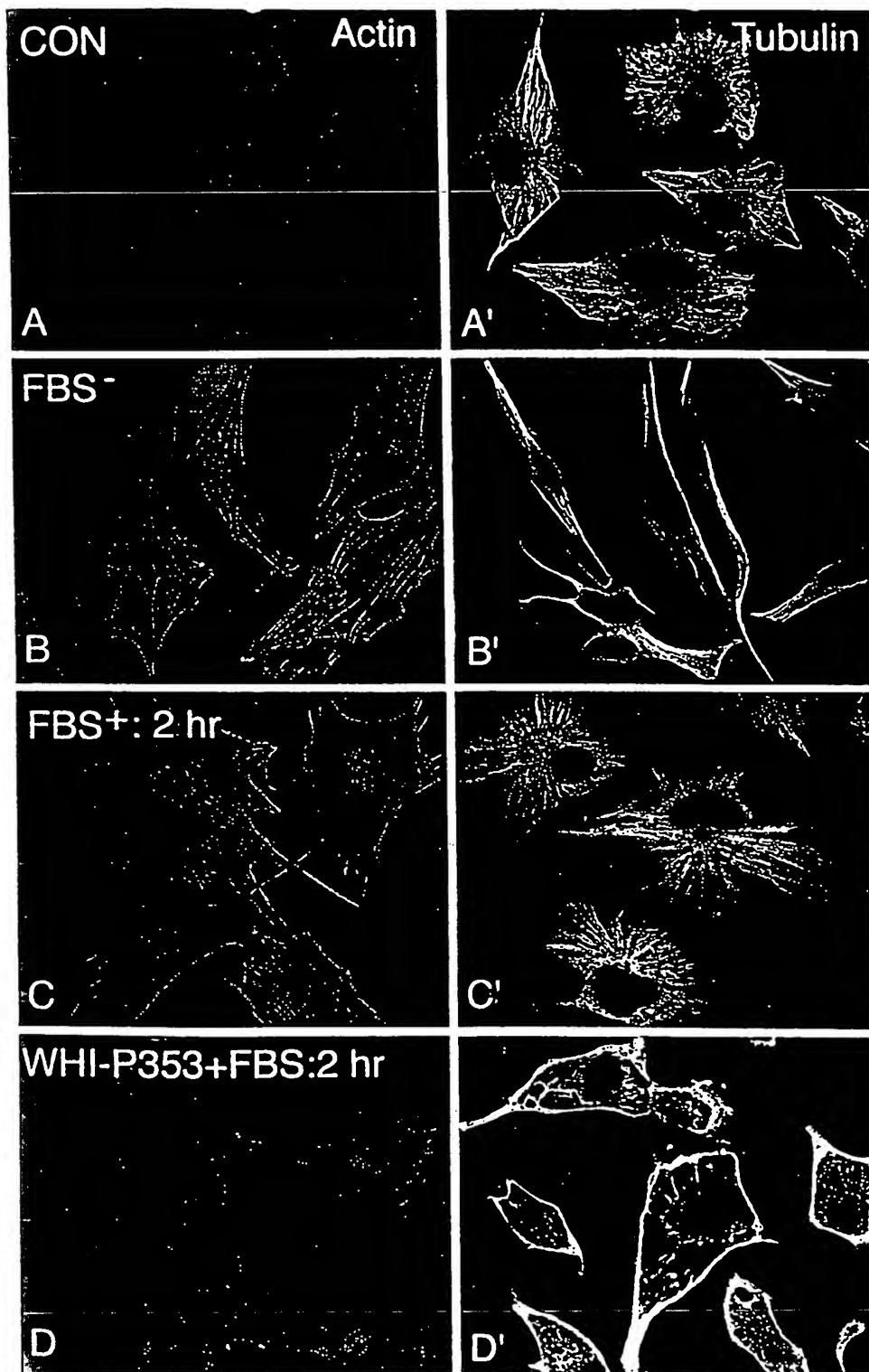
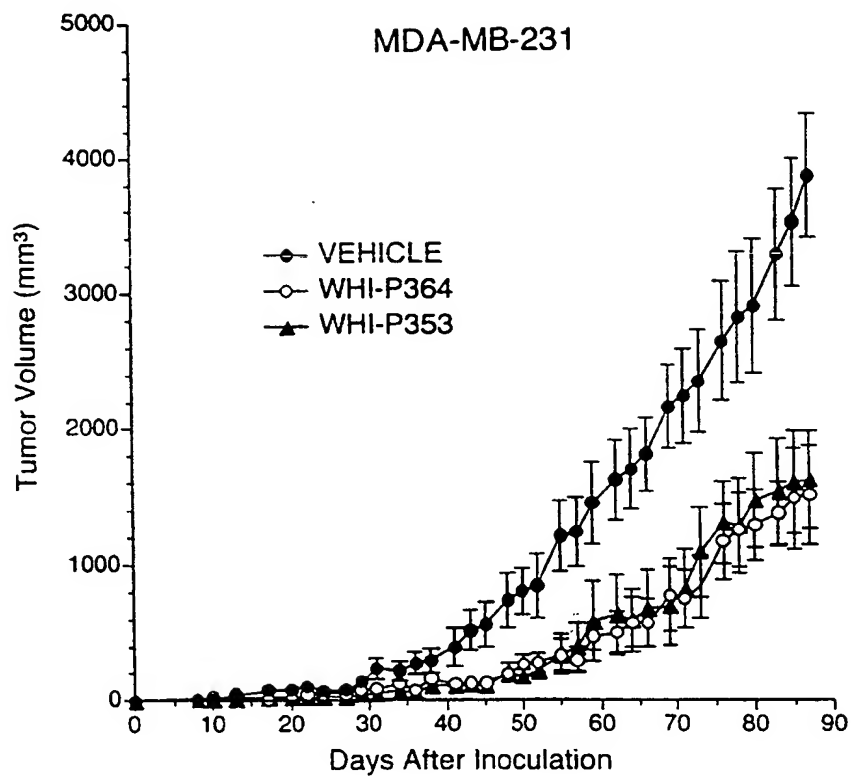


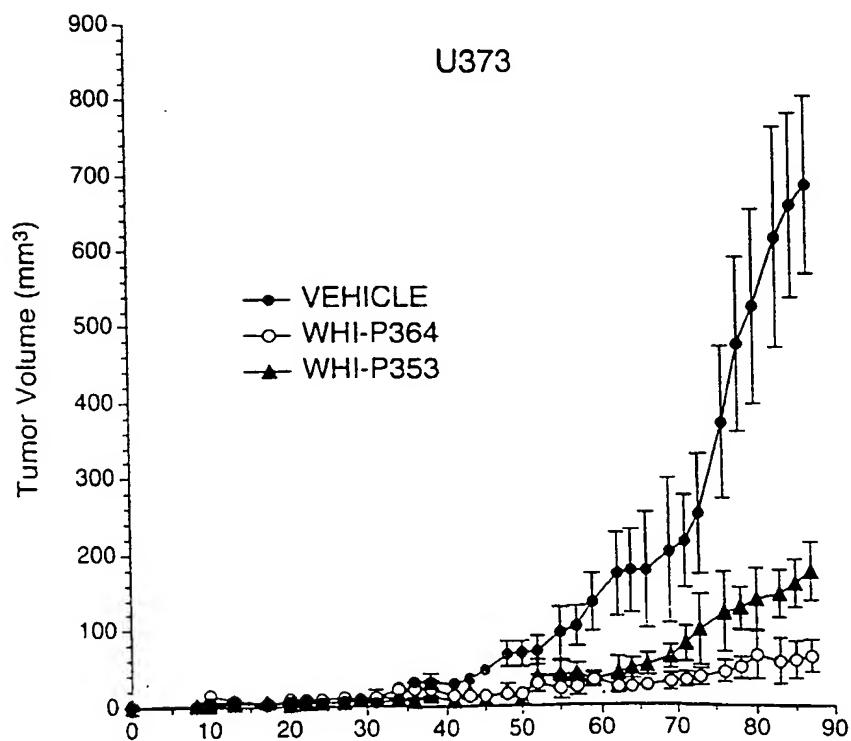
Fig 9



10A

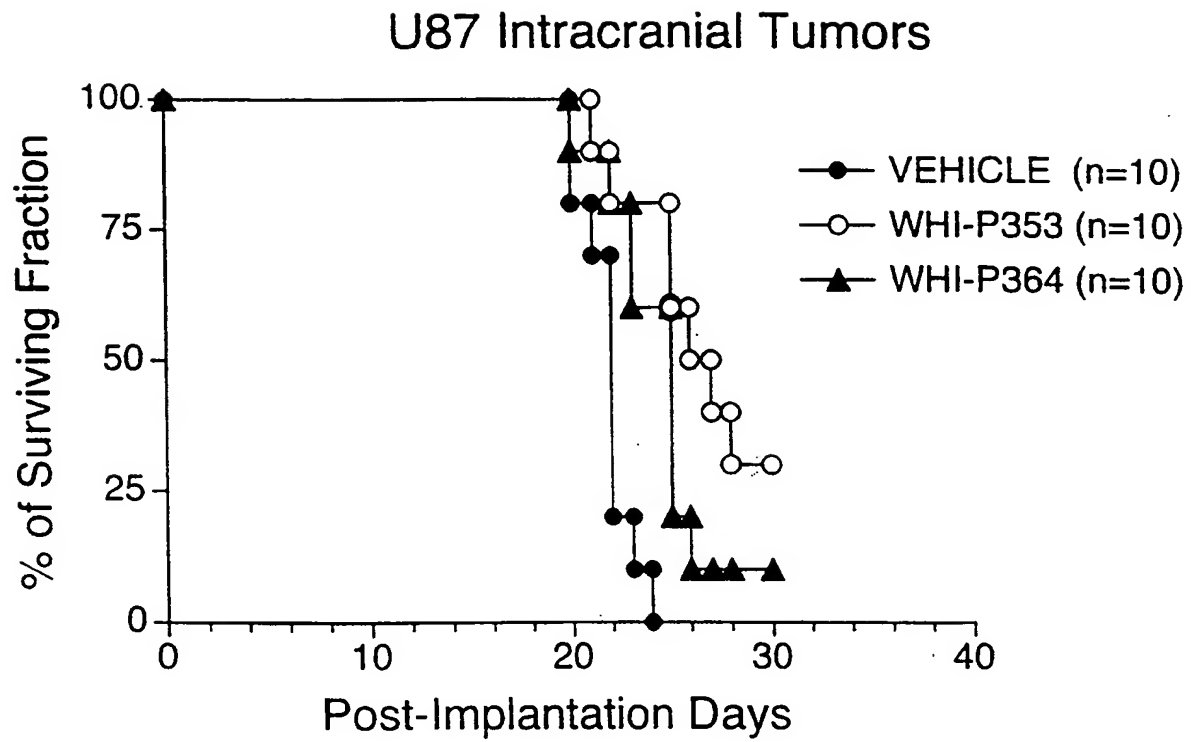


10B





(OC



## INTERNATIONAL SEARCH REPORT

Int. J. Application No

PCT/US 00/06902

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/94 A61K31/517 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

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X	EP 0 566 226 A (ZENECA) 20 October 1993 (1993-10-20) claims; table II & US 5 457 105 A 10 October 1995 (1995-10-10) cited in the application ---	1-3, 13, 14
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

10 July 2000

Date of mailing of the international search report

19/07/2000

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Authorized officer

Francois, J

## INTERNATIONAL SEARCH REPORT

Int'l. Application No.

PCT/US 00/06902

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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